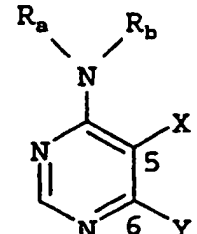




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<p>(21) International Application Number: PCT/EP00/02229</p> <p>(22) International Filing Date: 14 March 2000 (14.03.00)</p> <p>(30) Priority Data: 199 11 510.9 15 March 1999 (15.03.99) DE</p> <p>(71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM PHARMA KG [DE/DE]; D-55216 Ingelheim/Rhein (DE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HIMMELSBACH, Frank [DE/DE]; Ahornweg 16, D-88441 Mittelbiberach (DE). LANGKOPF, Elke [DE/DE]; Im Schloss 3, D-88447 Warthausen (DE). BLECH, Stefan [DE/DE]; Müllerweg 9, D-88447 Warthausen (DE). JUNG, Birgit [DE/DE]; Mühlstrasse 23, D-55270 Schwabenheim (DE). METZ, Thomas [DE/AT]; Traungasse 6/5, A-1030 Vienna (AT). SOLCA, Flavio [CH/AT]; Fimbinger-gasse 1/9, A-1230 Vienna (AT).</p> <p>(74) Agent: LAUDIEN, Dieter; Boehringer Ingelheim GmbH, B Patente, D-55216 Ingelheim/Rhein (DE).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>	
<p>(54) Title: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, THEIR USE AND PROCESSES FOR PREPARING THEM</p>		
<p>(57) Abstract</p> <p>The present invention relates to bicyclic heterocyclic compounds of general formula (I) wherein R_a, R_b, X and Y are defined as in claim 1, the tautomers, stereoisomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosinekinases, their use in treating diseases, particularly tumour diseases, diseases of the lung and airways and the preparation thereof.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

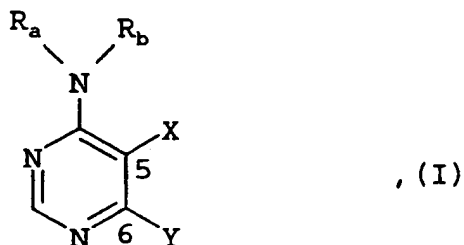
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Bicyclic heterocycles, pharmaceutical compositions containing these compounds, their use and processes for preparing them

The present invention relates to bicyclic heterocyclic compounds of general formula



the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases, their use in treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract and the preparation thereof.

In the above general formula I

R_a denotes a hydrogen atom or a C_{1-4} -alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4} -alkyl, hydroxy, C_{1-4} -alkoxy, C_{3-6} -cycloalkyl, C_{4-6} -cycloalkoxy, C_{2-5} -alkenyl or C_{2-5} -alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3,5}-alkenyloxy or C_{3,5}-alkynyloxy group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C_{1,4}-alkylsulphenyl, C_{1,4}-alkylsulphinyl, C_{1,4}-alkylsulphonyl, C_{1,4}-alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1,4}-alkyl groups, whilst the substituents may be identical or different,

or R₁ together with R₂, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH-, -CH=CH-NH or -CH=N-NH group and

R₃ denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1,4}-alkyl, trifluoromethyl or C_{1,4}-alkoxy group,

X and Y together denote a

-N=C(-A-B)-CH=CH-,
 -CH=N-C(-A-B)=CH-,
 -CH=C(-A-B)-N=CH-,
 -CH=CH-C(-A-B)=N-,
 -N=C(-A-B)-N=CH- or
 -CH=N-C(-A-B)=N bridge, wherein

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $-O-C_{1-8}$ -alkylene, $-O-C_{4-7}$ -cycloalkylene, $-O-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene, $-O-C_{4-7}$ -cycloalkylene- C_{1-3} -alkylene or $-O-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene- C_{1-3} -alkylene group, whilst the oxygen atom of the abovementioned group in each case is linked to the bicyclic heteroaromatic ring,

an $-NR_4-C_{1-8}$ -alkylene, $-NR_4-C_{3-7}$ -cycloalkylene, $-NR_4-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene, $-NR_4-C_{3-7}$ -cycloalkylene- C_{1-3} -alkylene or $-NR_4-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene- C_{1-3} -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a C_{1-4} -alkyl group,

an oxygen atom which is linked to a carbon atom of the group B,

an $-NR_4-C_{4-7}$ -cycloalkylene- $NH-SO_2-C_{1-4}$ -alkylene or $-NR_4-C_{4-7}$ -cycloalkylene- $N(C_{1-4}$ -alkyl)- SO_2-C_{1-4} -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and R_4 is as hereinbefore defined,

an $-NR_4$ group, where the latter is linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

an azetidinylene, pyrrolidinylene, piperidinylene or hexahydroazepinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an azetidinylene- $C_{1,3}$ -alkylene, pyrrolidinylene- $C_{1,3}$ -alkylene, piperidinylene- $C_{1,3}$ -alkylene or hexahydroazepinylene- $C_{1,3}$ -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene or 1,4-homopiperazinylene group, these groups each being linked to a carbon atom of the group B,

a 1,4-piperazinylene- $C_{1,3}$ -alkylene or 1,4-homopiperazinylene- $C_{1,3}$ -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -azetidinylene, $-NR_4$ -pyrrolidinylene, $-NR_4$ -piperidinylene or $-NR_4$ -hexahydroazepinylene group, whilst the $-NR_4$ - moiety of the abovementioned groups is linked in each case to the bicyclic heteroaromatic ring and in each case the cyclic nitrogen atom of the abovementioned groups is linked to a carbon atom of the group B,

an $-NR_4$ -azetidinylene- $C_{1,3}$ -alkylene, $-NR_4$ -pyrrolidinylene- $C_{1,3}$ -alkylene, $-NR_4$ -piperidinylene- $C_{1,3}$ -alkylene or $-NR_4$ -hexahydroazepinylene- $C_{1,3}$ -alkylene group, whilst in each case the $-NR_4$ - moiety of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned groups is in each case linked to the alkylene moiety,

an $-NR_4$ - $C_{3,7}$ -cycloalkylenecarbonyl group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

an $-NR_4$ - $C_{3,7}$ -cycloalkylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring

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and the nitrogen atom of the carbonylamino moiety, which may additionally be substituted by a C_{1-4} -alkyl group, is linked to a carbon atom of the group B,

an $-NR_4-C_{1-7}$ -cycloalkylenecarbonylamino- C_{1-3} -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety may additionally be substituted by a C_{1-4} -alkyl group,

an azetidinylenecarbonyl, pyrrolidinylencarbonyl, piperidinylencarbonyl or hexahydroazepinylenecarbonyl group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the carbonyl group in each case is linked to a nitrogen atom of the group B,

an azetidinylenecarbonylamino, pyrrolidinylencarbonylamino, piperidinylencarbonylamino or hexahydroazepinylenecarbonylamino group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety, which may additionally be substituted by a C_{1-4} -alkyl group, is linked to a carbon atom of the group B, an azetidinylenecarbonylamino- C_{1-3} -alkylene, pyrrolidinylencarbonylamino- C_{1-3} -alkylene, piperidinylencarbonylamino- C_{1-3} -alkylene or hexahydroazepinylenecarbonylamino- C_{1-3} -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety may additionally be substituted by a C_{1-4} -alkyl group, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one

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or two $C_{1,2}$ -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group, whilst

R_5 denotes a hydrogen atom,

a $C_{1,4}$ -alkyl group, which may be substituted by a hydroxy, $C_{1,4}$ -alkoxy, R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, amino, $C_{1,4}$ -alkylamino or di- $(C_{1,4}$ -alkyl)-amino group or by a 4 to 7-membered alkyleneimino group, whilst in the abovementioned 6 to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N- $(C_{1,4}$ -alkyl)-imino group,

a $C_{3,7}$ -cycloalkyl or $C_{3,7}$ -cycloalkyl- $C_{1,3}$ -alkyl group,

R_6 , R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom,

a $C_{1,8}$ -alkyl group which may be substituted by a hydroxy, $C_{1,4}$ -alkoxy, amino, $C_{1,4}$ -alkylamino or di- $(C_{1,4}$ -alkyl)-amino group or by a 4 to 7-membered alkyleneimino group, whilst in the abovementioned 6 to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N- $(C_{1,4}$ -alkyl)-imino group,

a $C_{4,7}$ -cycloalkyl group optionally substituted by one or two methyl groups,

a $C_{3,5}$ -alkenyl or $C_{3,5}$ -alkynyl group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a $C_{3,7}$ -cycloalkyl- $C_{1,4}$ -alkyl, aryl, aryl- $C_{1,4}$ -alkyl or $R_6CO-O-(R_6CR_4)$ group, whilst

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R_c and R_d , which may be identical or different, in each case denote a hydrogen atom or a C_{1-4} -alkyl group and

R_e denotes a C_{1-4} -alkyl, C_{3-7} -cycloalkyl, C_{1-4} -alkoxy or C_{5-7} -cycloalkoxy group,

and R_f denotes a C_{1-4} -alkyl, aryl or aryl- C_{1-4} -alkyl group,

a 4 to 7-membered alkyleneimino group which is substituted by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined and

R_{10} denotes a hydrogen atom, a C_{1-4} -alkyl, formyl, C_{1-4} -alkylcarbonyl or C_{1-4} -alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5 to 7-membered rings are each additionally substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group A,

a C_{5-7} -cycloalkyl group which is substituted by an amino, C_{1-4} -alkylamino or di- $(C_{1-4}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a C_{5-7} -cycloalkyl group wherein a methylene group is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group and in each case two hydrogen atoms in the cycloalkyl moiety are replaced by a straight-chained alkylene bridge, this bridge containing 2 to 6 carbon atoms, if the two hydrogen atoms are located at the same carbon atom, or contains 1 to 5 carbon atoms if the two hydrogen atoms are located at adjacent carbon atoms, or contains 2 to 4 carbon atoms, if the two hydrogen atoms are located at carbon atoms which are separated by one atom, whilst R_6 to R_9 are as hereinbefore defined,

or A together with B denotes a 1-azetidiny group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C_{4-6} -alkylene bridge, whilst in each case

a methylene group in the C_{4-6} -alkylene bridge is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]-imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group wherein R_6 to R_9 are as hereinbefore defined,

a 1-pyrrolidinyl, 1-piperidinyl or 1-azacyclohept-1-yl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C_{3-6} -alkylene bridge, whilst in each case a methylene group in the C_{3-6} -alkylene bridge is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group which are substituted in each case by an amino, C_{1-4} -alkylamino or di- $(C_{1-4}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

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whilst by the aryl moieties mentioned in the definition of the abovementioned groups is meant a phenyl group which may in each case be monosubstituted by R_{11} , mono-, di- or trisubstituted by R_{12} or monosubstituted by R_{11} and additionally mono- or disubstituted by R_{12} , whilst the substituents may be identical or different and

R_{11} may denote a cyano, carboxy, C_{1-4} -alkoxycarbonyl, aminocarbonyl, C_{1-4} -alkylaminocarbonyl, di- $(C_{1-4}$ -alkyl)-aminocarbonyl, C_{1-4} -alkylsulphenyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkylsulphonyl, hydroxy, C_{1-4} -alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, C_{1-4} -alkylcarbonylamino, N- $(C_{1-4}$ -alkyl)- C_{1-4} -alkylcarbonylamino, C_{1-4} -alkylsulphonylamino, N- $(C_{1-4}$ -alkyl)- C_{1-4} -alkylsulphonylamino, aminosulphonyl, C_{1-4} -alkylaminosulphonyl or di- $(C_{1-4}$ -alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N- $(C_{1-4}$ -alkyl)-imino group, and

R_{12} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4} -alkyl, trifluoromethyl or C_{1-4} -alkoxy group or

two R_{12} groups, if they are bound to adjacent carbon atoms, together denote a C_{3-5} -alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group.

Preferred compounds of the above general formula I are those wherein R_a , R_b , X and Y are as hereinbefore defined, with the proviso that

A does not denote an $-NR_4-C_{4-7}$ -cycloalkylene-NH-SO₂- C_{1-4} -alkylene or $-NR_4-C_{4-7}$ -cycloalkylene-N $(C_{1-4}$ -alkyl)-SO₂- C_{1-4} -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned groups in each

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case is linked to the bicyclic heteroaromatic ring and R_4 is as hereinbefore defined, and

does not denote an azetidinylene, pyrrolidinylene, piperidinylene or hexahydroazepinylene group substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

the tautomers, stereoisomers and salts thereof.

Particularly preferred compounds of general formula I are those wherein

R_4 denotes a hydrogen atom,

R_5 denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

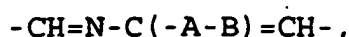
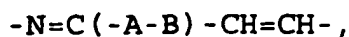
a methyl, trifluoromethyl, ethynyl or amino group,

a phenyl, phenoxy, benzyl or benzyloxy group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-\text{CH}=\text{CH}-\text{NH}$ or $-\text{CH}=\text{N}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote a



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-CH=CH-C(-A-B)=N- ,
 -N=C(-A-B)-N=CH- or
 -CH=N-C(-A-B)=N- bridge, whilst

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $\text{-NR}_4\text{-C}_{1,4}\text{-alkylene}$, $\text{-NR}_4\text{-cyclohexylene}$, $\text{-NR}_4\text{-cyclohexylene-NH-SO}_2\text{-C}_{1,3}\text{-alkylene}$, $\text{-NR}_4\text{-C}_{1,3}\text{-alkylene-cyclohexylene}$, $\text{-NR}_4\text{-cyclohexylene-C}_{1,3}\text{-alkylene}$ or $\text{-NR}_4\text{-C}_{1,3}\text{-alkylene-cyclohexylene-C}_{1,3}\text{-alkylene}$ group, whilst the $\text{-NR}_4\text{-}$ moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and

R_4 denotes a hydrogen atom or a methyl group,

an -NR_4 group, the latter being linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

a pyrrolidinylene or piperidinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylene- $\text{C}_{1,3}\text{-alkylene}$ group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene or 1,4-homopiperazinylene group, these groups each being linked to a carbon atom of the group B,

a 1,4-piperazinylene- $\text{C}_{1,2}\text{-alkylene}$ or 1,4-homopiperazinylene- $\text{C}_{1,2}\text{-alkylene}$ group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -piperidinylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to a carbon atom of the group B,

an $-NR_4$ -piperidinylene- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to the alkylene moiety,

an $-NR_4$ -cyclohexylenecarbonyl group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring,

a piperidinylencarbonyl group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

a piperidinylencarbonylamino group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

a piperidinylenecarbonylamino- $C_{1,2}$ -alkylene group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two $C_{1,2}$ -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group, whilst

R_5 denotes a hydrogen atom or

a $C_{1,4}$ -alkyl group which may be substituted by an R_6O-CO group,

R_6 , R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom,

a $C_{1,8}$ -alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a 5-indanyl group or a benzyl group optionally substituted in the phenyl moiety by one or two methyl groups and

R_9 denotes a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R_6O-CO or $R_6O-CO-C_{1,4}$ -alkyl group wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by the group R_{10} and is ad-

ditionally substituted at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_{10} , which is additionally substituted in each case at a carbon atom by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a methyl, ethyl or $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

a C_{5-6} -cycloalkyl group which is substituted by an amino, C_{1-2} -alkylamino or di- $(C_{1-2}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

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or A and B together denote a 1-pyrrolidinyl or 1-piperidinyl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C₄₋₅-alkylene bridge, whilst in each case a methylene group in the C₄₋₅-alkylene bridge is replaced by an R₆O-CO-C₁₋₄-alkylene-imino group wherein R₆ is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted in each case by an amino, C₁₋₂-alkylamino or di-(C₁₋₂-alkyl)-amino group and by an R₆O-CO group, whilst R₆ is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO or R₆O-CO-C₁₋₄-alkyl group wherein R₆ and R₁₀ are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

particularly those compounds of general formula I wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R₁ to R₃, whilst

R₁ and R₂, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

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a methyl, trifluoromethyl, ethynyl or amino group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-\text{CH}=\text{CH}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote a

$-\text{N}=\text{C}(-\text{A}-\text{B})-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{CH}-$,
 $-\text{CH}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{C}(-\text{A}-\text{B})=\text{N}-$,
 $-\text{N}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$ or
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{N}-$ bridge, whilst

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $-\text{NR}_4-\text{C}_{1..4}$ -alkylene, $-\text{NR}_4$ -cyclohexylene, $-\text{NR}_4$ -cyclohexylene- $\text{NH}-\text{SO}_2-\text{C}_{1..3}$ -alkylene, $-\text{NR}_4$ -methylene-cyclohexylene, $-\text{NR}_4$ -cyclohexylene-methylene or $-\text{NR}_4$ -methylene-cyclohexylene-methylene group, whilst the $-\text{NR}_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a methyl group,

an $-\text{NR}_4$ group, the latter being linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

a pyrrolidinylene or piperidinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylene- $C_{1,2}$ -alkylene group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene group, this group being linked in each case to a carbon atom of the group B,

a 1,4-piperazinylene- $C_{1,2}$ -alkylene group, the cyclic nitrogen atom of the abovementioned group being linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -piperidinylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety is straight-chained and contains 1 to 4 carbon atoms, whilst

R_5 denotes a hydrogen atom,

a $C_{1,2}$ -alkyl group which may be substituted by an R_6O-CO group,

R_6 denotes a hydrogen atom,

a C₁₋₈-alkyl group,

a cyclopentyl, cyclohexyl, cyclopentylmethyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a 5-indanyl group or a benzyl group optionally substituted in the phenyl moiety by one or two methyl groups and

R₇, R₈ and R₉, which may be identical or different, in each case denote a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group wherein R₆ is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R₆O-CO-C₁₋₃-alkyl, (R₇O-PO-OR₈)-C₁₋₃-alkyl or (R₇O-PO-R₉)-C₁₋₃-alkyl group wherein R₆ to R₉ are as hereinbefore defined, and

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

or A and B together denote a 1-pyrrolidinyl or 1-piperidinyl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C₄₋₅-alkylene bridge, whilst in each case a methylene group in the C₄₋₅-alkylene bridge is replaced by an R₆O-CO-C₁₋₂-alkyleneimino group wherein R₆ is as hereinbefore defined,

a piperidino group which is substituted by an amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

the tautomers, stereoisomers and salts thereof.

Most particularly preferred compounds of the abovementioned general formula I are those wherein X and Y together denote an $-N=C(-A-B)-N=CH-$ bridge,

Particularly those compounds wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl or amino group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote an $-CH=CH-NH$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote an $-N=C(-A-B)-N=CH-$ bridge, whilst

the left-hand end of this bridge is linked to position 5 and the right-hand end of this bridge is linked to position 6 of the pyrimidine ring,

A denotes an $-NR_4-C_{1-3}$ -alkylene, $-NR_4$ -cyclohexylene or $-NR_4$ -cyclohexylene-NH-SO₂-ethylene group, whilst the $-NR_4$ -moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a methyl group,

an $-NR_4$ group, the latter being linked to a carbon atom of the group B and R_4 being as hereinbefore defined,

an optionally methyl-substituted pyrrolidinylene or piperidinylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylenemethylene group, whilst the cyclic nitrogen atom is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene group, this group being linked to a carbon atom of the group B, and

B denotes an R_5O-CO -alkylene- NR_5 group wherein the alkylene moiety is straight-chained and contains 1 to 4 carbon atoms, whilst

R_5 denotes a hydrogen atom,

a C_{1-2} -alkyl group which may be substituted by an R_5O-CO group,

R_6 denotes a hydrogen atom,

a C₁₋₄-alkyl, cyclohexyl, phenyl, benzyl or 5-indanyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst R₆ is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R₆O-CO-methyl or (R₇O-PO-OR₈)-methyl group wherein R₆ is as hereinbefore defined and

R₇ and R₈ in each case denotes a methyl or ethyl group,

a piperidinyll group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-methyl, (R₇O-PO-OR₈)-ethyl or (R₇O-PO-R₉)-methyl group wherein R₆ to R₉ are as hereinbefore defined and

R₉ denotes a methyl or ethyl group,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

or A and B together denote a piperidino group which is substituted by an amino group and by an R₆O-CO group, whilst R₆ is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R₆O-CO-C₁₋₂-alkyl group, wherein R₆ is as hereinbefore defined,

the tautomers, stereoisomers and salts thereof.

The following particularly preferred compounds of general formula I are mentioned by way of example:

- (1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{N-[(methoxycarbonyl)methyl]-N-methylamino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,
- (3) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine
- (4) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (5) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine
- (6) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (7) 4-[(4-amino-3,5-dichlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (8) 4-[(4-amino-3,5-dibromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (9) 4-[(indol-5-yl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,
- (10) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,
- (11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-{N',N'-bis[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimidine,

(14) 4-[(3-bromophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)-methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine,

(15) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine,

(17) 4-[(3-bromophenyl)amino]-6-({1-[(diethoxyphosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

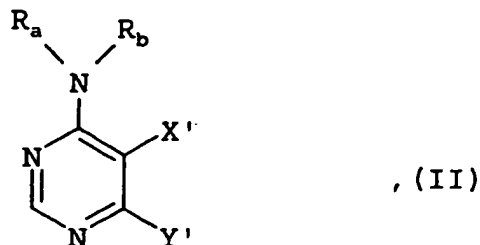
(18) 4-[(3-bromophenyl)amino]-6-[(1-{[(ethoxy)(methyl)phosphoryl]methyl}-piperidin-4-yl)amino]-pyrimido[5,4-d]pyrimidine,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[trans-4-(2-oxomorpholin-4-yl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

and the salts thereof.

The compounds of general formula I may be prepared, for example, by the following methods:

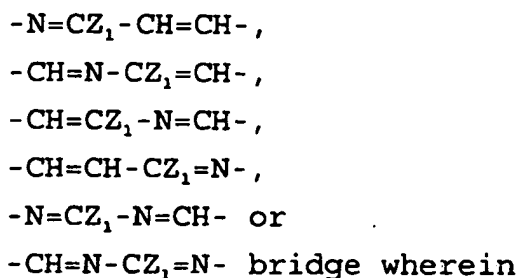
a) reacting a compound of general formula



wherein

R_a and R_b are as hereinbefore defined,

X' and Y' together denote a



Z_1 denotes an exchangeable group such as a halogen atom or a substituted sulphinyl or sulphonyl group, e.g. a chlorine or bromine atom, a methylsulphinyl, propylsulphinyl, phenylsulphinyl, benzylsulphinyl, methylsulphonyl, propylsulphonyl, phenylsulphonyl or benzylsulphonyl group, with a compound of general formula



wherein

A and B are as hereinbefore defined.

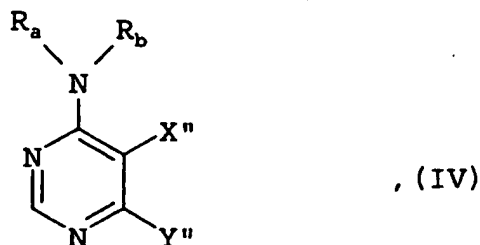
The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, sulfolane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst

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these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C.

b) In order to prepare a compound of general formula I wherein at least one of the groups R_6 to R_8 denote a hydrogen atom:

Converting a compound of general formula



wherein

R_a and R_b are as hereinbefore defined,

X'' and Y'' together denote a

-N=C(-A-B')-CH=CH-,
 -CH=N-C(-A-B')=CH-,
 -CH=C(-A-B')-N=CH-,
 -CH=CH-C(-A-B')=N-,
 -N=C(-A-B')-N=CH- or
 -CH=N-C(-A-B')=N- bridge wherein

A is as hereinbefore defined and

B' has the meanings given for B hereinbefore with the proviso that B' contains an R_6O-CO , $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$ group, wherein R_9 is as hereinbefore defined and at least one of the groups R_6 to R_8 does not represent a hydrogen atom, by hydrolysis, treating with acids, thermolysis or hydrogenolysis into a compound of general formula I, wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom.

For example, functional derivatives of the carboxyl group such as the unsubstituted or substituted amides, esters, thioesters, trimethylsilylestere, orthoesters, iminoesters, amidines or anhydrides, or the nitrile group may be converted by hydrolysis into a carboxyl group,

ester with tertiary alcohols, e.g. the tert.butylester, may be converted by treatment with an acid or thermolysis into a carboxyl group and

esters with aralkanols, e.g. the benzylesters, may be converted by hydrogenolysis into a carboxyl group.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

Under the reaction conditions mentioned above, any N-acylamino or N-acylimino groups present such as an N-trifluoroacetyl-imino group may be converted into the corresponding amino or imino groups. Moreover, any alcoholic hydroxy groups present may be converted, during the treatment with an organic acid such as trichloroacetic acid or trifluoroacetic acid, into a corresponding acyloxy group such as the trifluoroacetox group.

If B' in a compound of formula IV contains a cyano or amino-carbonyl group, these groups may also be converted into the carboxyl group with a nitrite, e.g. sodium nitrite, in the

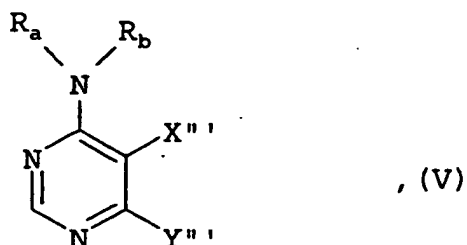
presence of an acid such as sulphuric acid, which is conveniently used as the solvent at the same time, at temperatures between 0 and 50°C.

If B' in a compound of formula IV denotes the tert.butyloxy-carbonyl group, for example, the tert.butyl group may also be cleaved by treating with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane preferably at temperatures between -10 and 120°C, e.g. at temperatures between 0 and 60°C, or optionally thermally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40 and 120°C. Under the reaction conditions mentioned, any N-tert.butyloxycarbonylamino or N-tert.butyloxycarbonylimino groups present may be converted into the corresponding amino or imino groups.

If B' in a compound of formula IV contains the benzyloxycarbonyl group, for example, the benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide preferably at temperatures between 0 and 50°C, e.g. ambient temperature, and at a hydrogen pressure of 1 to 5 bar. During the hydrogenolysis other groups may be converted at the same time, e.g. a nitro group into an amino group, a benzyloxy group into a hydroxy group and a N-benzylamino, N-benzylimino, N-benzyl-oxy-carbonylamino or N-benzyl-oxy-carbonylimino group into a corresponding amino or imino group.

c) In order to prepare a compound of general formula I wherein A denotes an $-\text{NR}_4-\text{C}_{4..}-\text{cycloalkylene}-\text{NH}-\text{SO}_2-\text{CH}_2\text{CH}_2$ or $-\text{NR}_4-\text{C}_{4..}-\text{cycloalkylene}-\text{N}(\text{C}_{1..4}-\text{alkyl})-\text{SO}_2-\text{CH}_2\text{CH}_2$ group and B denotes an $\text{R}_6\text{O}-\text{CO}-\text{C}_{1..6}-\text{alkylene}-\text{NR}_5$ group, whilst R_4 to R_6 are as hereinbefore defined:

reacting a compound of general formula

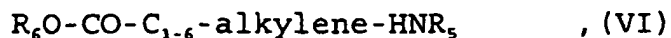


wherein

R_a and R_b are as hereinbefore defined,
 X'' and Y'' together denote a

$-\text{N}=\text{C}(-\text{A}'-\text{H})-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{N}-\text{C}(-\text{A}'-\text{H})=\text{CH}-$,
 $-\text{CH}=\text{C}(-\text{A}'-\text{H})-\text{N}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{C}(-\text{A}'-\text{H})=\text{N}-$,
 $-\text{N}=\text{C}(-\text{A}'-\text{H})-\text{N}=\text{CH}-$ or
 $-\text{CH}=\text{N}-\text{C}(-\text{A}'-\text{H})=\text{N}-$ bridge wherein

A' denotes an $-\text{NR}_4-\text{C}_{4..}-\text{cycloalkylene}-\text{NH}-\text{SO}_2-\text{CH}=\text{CH}_2$ or $-\text{NR}_4-\text{C}_{4..}-\text{cycloalkylene}-\text{N}(\text{C}_{1..4}-\text{alkyl})-\text{SO}_2-\text{CH}=\text{CH}_2$ group, whilst R_4 is as hereinbefore defined, with a compound of general formula



wherein

R_5 and R_6 are as hereinbefore defined.

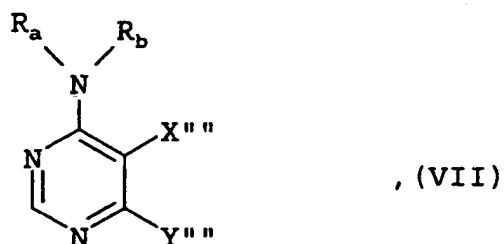
The reaction is preferably carried out in a solvent such as methanol, ethanol or isopropanol in the presence of a base

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such as N-ethyl-diisopropylamine at temperatures between 0 and 100°C, but preferably at the boiling temperature of the reaction mixture.

d) In order to prepare a compound of general formula I wherein B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst in each case R_5 and R_6 are as hereinbefore defined:

reacting a compound of general formula



wherein

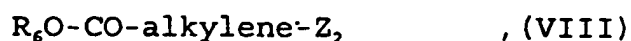
R_a and R_b are as hereinbefore defined,

X''' and Y''' together denote a

$-N=C(-A-B'')-CH=CH-$,
 $-CH=N-C(-A-B'')=CH-$,
 $-CH=C(-A-B'')-N=CH-$,
 $-CH=CH-C(-A-B'')=N-$,
 $-N=C(-A-B'')-N=CH-$ or
 $-CH=N-C(-A-B'')=N-$ bridge, wherein

A is as hereinbefore defined and

B" denotes an R_5NH group wherein R_5 is as hereinbefore defined, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, with a compound of general formula



wherein

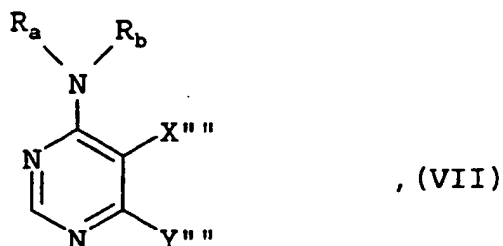
the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 in each case is as hereinbefore defined, and Z_2 denotes an exchangeable group such as a halogen atom or a substituted sulphonyloxy group, e.g. a chlorine or bromine atom, a methylsulphonyloxy, propylsulphonyloxy, phenylsulphonyloxy or benzylsulphonyloxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, sulfolane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine or N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution conveniently at temperatures between -20 and $200^\circ C$, preferably at temperatures between 0 and $150^\circ C$.

e) In order to prepare a compound of general formula I wherein B denotes an $(R_7O-PO-OR_8)-CH_2-NR_5$ or $(R_7O-PO-R_9)-CH_2-NR_5$ group, a piperazino or homopiperazino group substituted in the 4 position by an $(R_7O-PO-OR_8)-CH_2$ or $(R_7O-PO-R_9)-CH_2$ group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by a $(R_7O-PO-OR_8)-CH_2$ or $(R_7O-PO-R_9)-$

CH₂ group, whilst in each case R₅ and R₇ to R₉ are as hereinbefore defined:

reacting a compound of general formula



wherein

R_a and R_b are as hereinbefore defined,

X'' and Y'' together denote a

-N=C(-A-B'')-CH=CH-,
 -CH=N-C(-A-B'')=CH-,
 -CH=C(-A-B'')-N=CH-,
 -CH=CH-C(-A-B'')=N-,
 -N=C(-A-B'')-N=CH- or
 -CH=N-C(-A-B'')=N- bridge wherein

A is as hereinbefore defined and

B'' denotes an R₅NH group wherein R₅ is as hereinbefore defined, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, with formaldehyde or one of the derivatives thereof and a compound of general formula



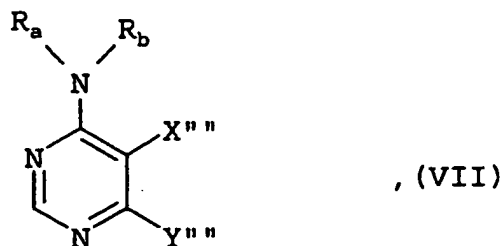
wherein .

R₇ to R₉ are as hereinbefore defined.

The reaction is conveniently carried out in a solvent or mixture of solvents such as dioxane, tetrahydrofuran, benzene or toluene at temperatures between 50 and 150°C, preferably at the boiling temperature of the solvent used.

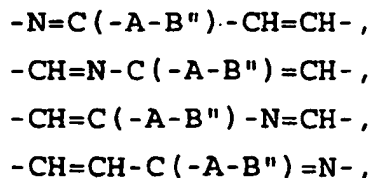
f) In order to prepare a compound of general formula I wherein B denotes an $R_6O-CO-CH_2CH_2-NR_5$ group wherein the $-CH_2CH_2-$ moiety may be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-CH_2CH_2$ group wherein the $-CH_2CH_2-$ moiety may in each case additionally be substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-CH_2CH_2$ group wherein the $-CH_2CH_2-$ moiety may in each case additionally be substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group and R_5 and R_6 in each case are as hereinbefore defined:

reacting a compound of general formula

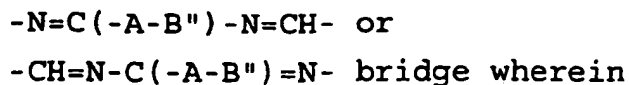


wherein

R_a and R_b are as hereinbefore defined,
 X'' and Y'' together denote a



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A is as hereinbefore defined and

B'' denotes an R_5NH group wherein R_5 is as hereinbefore defined, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, with an acrylate of general formula



wherein

the vinyl moiety may be substituted by one or two C_{1-2} -alkyl groups or by an $\text{R}_6\text{O}-\text{CO}$ or $\text{R}_6\text{O}-\text{CO}-\text{C}_{1-2}$ -alkyl group and R_6 in each case is as hereinbefore defined.

The reaction is preferably carried out in a solvent such as methanol, ethanol or isopropanol at temperatures between 50 and 100°C , but preferably at the boiling temperature of the reaction mixture.

Moreover, a compound of general formula I wherein B denotes a piperidinyl group substituted in position 1 by a $(\text{R}_7\text{O}-\text{PO}-\text{OR}_8)-\text{CH}_2\text{CH}_2$ group may also be prepared, for example, by reacting a corresponding compound containing a piperidinyl group unsubstituted in position 1 with a corresponding vinylphosphonic acid derivative.

If according to the invention a compound of general formula I is obtained which contains a carboxy or hydroxyphosphoryl group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained wherein B denotes an optionally substituted N-(2-hydroxyethyl)-glycine or N-(2-hydroxyethyl)-glycine ester group, this group may be

converted by cyclisation into a corresponding 2-oxo-morpholino compound.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or particularly advantageously in a corresponding alcohol, optionally in the presence an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenyl-phosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent ester formation may also be carried out by reacting a compound which contains a carboxy or hydroxyphosphoryl group with a corresponding alkyl halide.

The subsequent intramolecular cyclisation is optionally carried out in a solvent or mixture of solvents such as acetonitrile, methylene chloride, tetrahydrofuran, dioxane or toluene in the presence an acid such as hydrochloric acid or p-toluenesulphonic acid at temperatures between -10 and 120°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, phosphono, O-alkyl-phosphono, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

protecting groups for a phosphono group may be an alkyl group such as the methyl, ethyl, isopropyl or n-butyl group, the phenyl or benzyl group, and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

A single alkyl group may be cleaved from an O,O'-dialkylphosphono group with sodium iodide, for example, in a solvent such as acetone, methylethylketone, acetonitrile or dimethylformamide at temperatures between 40 and 150°C, but preferably at temperatures between 60 and 100°C.

Both alkyl groups may be cleaved from an O,O'-dialkylphosphono group with iodotrimethylsilane, bromotrimethylsilane or chlorotrimethylsilane/sodium iodide, for example, in a solvent such as methylene chloride, chloroform or acetonitrile at temperatures between 0°C and the boiling temperature of the reaction mixture, but preferably at temperatures between 20 and 60°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures

may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy, hydroxyphosphoryl, sulpho or 5-tetrazolyl group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to XI used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature (cf. Examples I to XX).

For example, a starting compound of general formulae II, IV, V and VII is obtained by successively replacing exchangeable groups in a corresponding compound which is in turn obtained by known methods, e.g. by introducing halogen into a corresponding hydroxy compound.

A compound of general formula III is obtained by methods known from the literature, for example by reductive alkylation of a corresponding ketone, by alkylation of a corresponding amine or by adding an amine to a corresponding alkenyl compound and optionally subsequently cleaving any protecting groups used.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and their physiologically acceptable salts have valuable pharmacological properties, particularly an inhibiting effect on signal transduction

mediated by the Epidermal Growth Factor receptor (EGF-R), whilst this may be achieved for example by inhibiting ligand bonding, receptor dimerisation or tyrosine kinase itself. It is also possible to block the transmission of signals to components located further down.

The biological properties of the new compounds were investigated as follows:

The inhibition of the EGF-R-mediated signal transmission can be demonstrated e.g. with cells which express human EGF-R and whose survival and proliferation depend on stimulation by EGF or TGF- α . A cell line of murine origin dependent on interleukin-3-(IL-3) which was genetically modified to express functional human EGF-R was used here. The proliferation of these cells known as F/L-HERc can therefore be stimulated either by murine IL-3 or by EGF (cf. von Rüden, T. et al. in EMBO J. 7, 2749-2756 (1988) and Pierce, J. H. et al. in Science 239, 628-631 (1988)).

The starting material used for the F/L-HERc cells was the cell line FDC-P₁, the production of which has been described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). Alternatively, however, other growth-factor-dependent cells may also be used (cf. for example Pierce, J. H. et al. in Science 239, 628-631 (1988), Shibuya, H. et al. in Cell 70, 57-67 (1992) and Alexander, W. S. et al. in EMBO J. 10, 3683-3691 (1991)). For expressing the human EGF-R cDNA (cf. Ullrich, A. et al. in Nature 309, 418-425 (1984)) recombinant retroviruses were used as described by von Rüden, T. et al., EMBO J. 7, 2749-2756 (1988), except that the retroviral vector LXS_N (cf. Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) was used for the expression of the EGF-R cDNA and the line GP+E86 (cf. Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as the packaging cell.

The test was performed as follows:

F/L-HERc cells were cultivated in RPMI/1640 medium (BioWhittaker), supplemented with 10 % foetal calf serum (FCS, Boehringer Mannheim), 2 mM glutamine (BioWhittaker), standard antibiotics and 20 ng/ml of human EGF (Promega), at 37°C and 5% CO₂. In order to investigate the inhibitory activity of the compounds according to the invention, 1.5×10^4 cells per well were cultivated in triplicate in 96-well plates in the above medium (200 μ l), the cell proliferation being stimulated with either EGF (20 ng/ml) or murine IL-3. The IL-3 used was obtained from culture supernatants of the cell line X63/0 mIL-3 (cf. Karasuyama, H. et al. in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures were incubated for 48 hours at 37°C.

In order to determine the inhibitory activity of the compounds according to the invention the relative cell number was measured in O.D. units using the Cell Titer 96TM Aqueous Non-Radioactive Cell Proliferation Assay (Promega). The relative cell number was calculated as a percentage of the control (F/LHERc cells without inhibitor) and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC₅₀) was derived therefrom. The following results were obtained:

Compound (Example no.)	Inhibition of EGF- dependent proliferation IC ₅₀ [nM]
1	840
1(3)	320
1(6)	2300
1(8)	1450
1(9)	820
1(10)	2510
1(11)	2320
2(1)	15
2(7)	60
2(10)	2040
2(12)	810
2(13)	1030
2(14)	1150
2(15)	1760
2(17)	30
2(19)	129
2(23)	25
2(24)	73
2(26)	21
2(27)	77
2(28)	26
3(4)	58
3(5)	20
3(10)	16
3(12)	103
3(16)	20
3(17)	17
3(18)	40
4(1)	40
4(2)	40
7	122

The compounds of general formula I according to the invention thus inhibit the signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosinekinases. These are e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and the abnormal proliferation of vascular endothelial cells (neovascularisation).

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosinekinases, e.g. in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α 1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosinekinases, such as may be found e.g. in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Ménétrier's disease, secreting adenomas and protein loss syndrome, and also for treating nasal polyps and polyps of the gastrointestinal tract of various origins such as e.g. villous or adenomatous polyps of the large bowel, but also polyps in familial polyposis coli, intestinal polyps in Gardner's syndrome, polyps throughout the entire gastrointestinal tract in Peutz-Jeghers syndrome, in inflammatory pseudopolyps, juvenile polyps, Colitis cystica profunda and Pneumatosis cystoides intestinales.

Moreover, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat kidney diseases, particularly in cystic changes such as cystic kidneys, for treating renal cysts which may be idiopathic in origin or occur in syndromes such as e.g. tuberculous sclerosis, in von-Hippel-Lindau Syndrome, in nephronophthisis and spongy kidney and other diseases caused by aberrant function of tyrosinekinases, such as e.g. epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of haematopoietic cells, etc.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastin), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or antiinflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion or antiinflammatory substances. These combinations may be administered either simultaneously or sequentially.

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intrarectal, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it:

Preparation of the starting products:

Example I4-amino-1-[(ethoxycarbonyl)methyl]-piperidine-dihydrochloride

Hydrogen chloride gas is passed through a solution of 2.36 g of 4-[(tert.butyloxycarbonyl)amino]-1-[(ethoxycarbonyl)-methyl]-piperidine in ethanol for about 10 minutes. The solution heats up significantly and after a short time a thick precipitate is formed. The suspension is refluxed for a further half hour, during which time the precipitate goes back into solution. The reaction mixture is concentrated by evaporation, taken up with toluene and again concentrated by evaporation. The residue is stirred with acetone, suction filtered and washed with acetone and diethylether. The almost colourless, crystalline product is dried in the desiccator.

Yield: 2.15 g of (100 % of theory),

melting point: 156°C (decomposition)

Mass spectrum (ESI⁺): m/z = 187 [M+H]⁺

The following compounds are obtained analogously to Example I:

(1) 4-amino-1-[(methoxycarbonyl)methyl]-piperidine x 4.4 tri-fluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

¹H-NMR (200 MHz, DMSO-d₆): * = 1.7-2.0 (m, 2H), 2.0-2.2 (m, 2H), 3.0-3.4 (m, 3H), 3.45-3.65 (m, 2H), 3.75 (s, 3H), 4.2 (s, 2H), 8.25 (br s, 3H)

Calc.:	C	29.94	H	3.05	N	4.16
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Found:	C	31.09	H	3.65	N	4.14
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(2) 4-amino-1-[(propyloxycarbonyl)methyl]-piperidine-dihydrochloride

melting point: 148-154°C (decomposition)

Mass spectrum (ESI⁺): m/z = 201 [M+H]⁺

(3) 4-amino-1-[(isopropoxyloxycarbonyl)methyl]-piperidine-dihydrochloride

melting point: 159-168°C

Mass spectrum (ESI⁺): m/z = 201 [M+H]⁺

(4) 4-amino-1-[(cyclohexyloxycarbonyl)methyl]-piperidine x 2 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

melting point: 133-138°C

Mass spectrum (ESI⁺): m/z = 241 [M+H]⁺

(5) 4-amino-1-[2-(methoxycarbonyl)ethyl]-piperidine-dihydrochloride

melting point: 213-215°C (decomposition)

Mass spectrum (ESI⁺): m/z = 187 [M+H]⁺

(6) 4-amino-1-[3-(methoxycarbonyl)propyl]-piperidine-dihydrochloride

melting point: 170-172°C

Mass spectrum (EI): m/z = 200 [M]⁺

(7) trans-4-amino-1-{N-[(methoxycarbonyl)methyl]-N-methyl-amino}-cyclohexane-dihydrochloride

R_f value: 0.15 (silica gel, methylene chloride/methanol/concentrated, aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): m/z = 201 [M+H]⁺

(8) trans-4-amino-1-{N-[2-(methoxycarbonyl)ethyl]-N-methyl-amino}-cyclohexane-dihydrochloride

R_f value: 0.16 (silica gel, methylene chloride/methanol/concentrated, aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): m/z = 215 [M+H]⁺

(9) *trans*-4-amino-1-{N-[3-(methoxycarbonyl)propyl]-N-methyl-amino}-cyclohexane-dihydrochloride

melting point: 170-190°C (decomposition)

Mass spectrum (ESI⁺): m/z = 229 [M+H]⁺

(10) 1-{1-[2-(ethoxycarbonyl)ethyl]-piperidin-4-yl}-piperazine x 3 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

melting point: 183-186°C (decomposition)

Calc.:	C	39.29	H	4.95	N	6.87
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Found:	C	39.01	H	4.97	N	7.03
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(11) 4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidine x 2 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

(12) 4-{[2-(methoxycarbonyl)-piperidine-1-yl]methyl}-piperidine x 2 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

R_f value: 0.30 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

(13) 4-{[2-(methoxycarbonyl)-pyrrolidin-1-yl]methyl}-piperidine x 2 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

R_f value: 0.13 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

(14) 4-({4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}methyl)-piperidine x 2 trifluoroacetic acid (carried out with trifluoroacetic acid in methylene chloride)

R_f value: 0.18 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

(15) *trans*-4-amino-1-{N-[(ethoxycarbonyl)methyl]-N-(2-hydroxy-2-methyl-prop-1-yl)-amino}-cyclohexane x 2 trifluoroacetic acid (The reaction was carried out with trifluoroacetic acid in methylene chloride.)

R_f: 0.75 (reversed phase TLC-plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI⁺): m/z = 273 [M+H]⁺

Example II

1-[(ethoxycarbonyl)methyl]-4-(2-aminoethyl)-piperidine-dihydrochloride

1.0 g of 1-[(ethoxycarbonyl)methyl]-4-(cyanomethyl)-piperidine-hydrochloride is dissolved in 15 ml ethanol and 1.0 ml of ethanolic hydrochloric acid and hydrogenated in the presence of 0.15 g of palladium (10% on activated charcoal) as catalyst at 50°C and at a hydrogen pressure of 50 psi in a Parr apparatus until the calculated amount of hydrogen is taken up. The catalyst is filtered off and the filtrate is concentrated by evaporation. The residue is taken up in acetone and ethanolic hydrochloric acid is added dropwise until the dihydrochloride is precipitated. The precipitate is suction filtered, washed with acetone and diethylether and dried in the desiccator.

Yield: 760 mg (66 % of theory),

R_f value: 0.22 (silica gel, toluene/dioxane/methanol/concentrated, aqueous ammonia solution = 20:50:20:2)

Example III

3-{4-[2-(methoxycarbonyl)ethyl]-piperidin-1-yl}-pyrrolidine-dihydrochloride

5.3 g of 4-[2-(methoxycarbonyl)ethyl]-piperidine and 2.07 g of sodium acetate are added to a solution of 4.4 g of N-benzyl-3-pyrrolidinone in 45 ml methanol. Then 1.61 g of sodium cyanoborohydride are added and the reaction mixture is stirred

for three days at ambient temperature. For working up the reaction mixture is concentrated by evaporation and the residue is stirred with saturated sodium hydrogen carbonate solution. The aqueous phase is extracted with ethyl acetate, the combined extracts are washed with water and saturated sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. The crude product is purified by chromatography over a silica gel column with methylene chloride/methanol (9:1).

Yield: 5.60 g (67 % of theory) of N-benzyl-3-{4-[2-(methoxycarbonyl)ethyl]-piperidin-1-yl}-pyrrolidine as a yellowish oil, R_f value: 0.54 (silica gel, methylene chloride/methanol = 9:1).

In order to cleave the benzyl protecting group 5.4 g of the product obtained are dissolved in 100 ml methanol, acidified with 1N hydrochloric acid and hydrogenated in the presence of 1.5 g of palladium (10 % on activated charcoal) at ambient temperature and at a hydrogen pressure of 50 psi in a Parr apparatus. The catalyst is filtered off, the filtrate is concentrated by evaporation and the brownish crystalline product is dried in the desiccator.

Yield: 5.10 g (100 % of theory),

R_f value: 0.56 (Reversed phase ready-made thin layer plate RP-8 (E. Merck), methanol/5% aqueous sodium chloride solution = 6:4).

Example IV

4-[(tert.butyloxycarbonyl)amino]-1-[(ethoxycarbonyl)methyl]-piperidine

1.36 ml of ethyl bromoacetate and 2.77 ml of triethylamine are added to 2.00 g of 4-[(tert.butyloxycarbonyl)amino]-piperidine in 15 ml acetonitrile at ambient temperature. The reaction mixture is stirred at 65°C for about two hours, during which time a clear solution is formed. The solvent is distilled off using a rotary evaporator, the residue is stirred with ice-cold water and made alkaline with a little potassium carbonate

solution. The precipitate thus formed is suction filtered and the aqueous phase is extracted with ethyl acetate. The combined extracts are washed with water and saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The residue is combined with the precipitate filtered off, washed with water and dried in the desiccator. Yield: 2.40 g (84 % of theory),
melting point: 76-79°C
Mass spectrum (ESI⁺): 309 [M+Na]⁺

The following compounds are obtained analogously to Example IV:

(1) 4-[(tert.butyloxycarbonyl)amino]-1-[(methoxycarbonyl)methyl]-piperidine

melting point: 96-98°C

R_f value: 0.21 (silica gel, cyclohexane/ethyl acetate = 1:1)

(2) 4-[(tert.butyloxycarbonyl)amino]-1-[(propyloxycarbonyl)methyl]-piperidine

melting point: 97-99°C

Mass spectrum (ESI⁺): 323 [M+Na]⁺

(3) 4-[(tert.butyloxycarbonyl)amino]-1-[(isopropyloxycarbonyl)methyl]-piperidine

melting point: 94-96°C

Mass spectrum (ESI⁺): 323 [M+Na]⁺

(4) 4-[(tert.butyloxycarbonyl)amino]-1-[(cyclohexyloxycarbonyl)methyl]-piperidine

melting point: 102-104°C

Mass spectrum (ESI⁺): 363 [M+Na]⁺

(5) 4-[(tert.butyloxycarbonyl)amino]-1-[3-(methoxycarbonyl)propyl]-piperidine

R_f value: 0.75 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): 301 [M+H]⁺

(6) *trans*-4-[(*tert*-butyloxycarbonyl)amino]-1-{N-[(methoxycarbonyl)methyl]-N-methylamino}-cyclohexane

R_f value: 0.65 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): 301 [M+H]⁺

(7) *trans*-4-[(*tert*-butyloxycarbonyl)amino]-1-{N-[3-(methoxycarbonyl)propyl]-N-methylamino}-cyclohexane

R_f value: 0.50 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): 329 [M+H]⁺

(8) 1-[(ethoxycarbonyl)methyl]-4-(cyanomethyl)-piperidine-hydrochloride (after reacting the crude product obtained to form the hydrochloride)

melting point: 131-136°C

R_f value: 0.67 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 95:5:1)

(9) *trans*-1-[(*tert*-Butyloxycarbonyl)amino]-4-{N-[(ethoxycarbonyl)methyl]-N-(2-hydroxy-2-methyl-prop-1-yl)-amino}-cyclohexane

R_f: 0.75 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:1)

Mass spectrum (ESI⁺): m/z = 373, 375 [M+H]⁺

Example V4-[(tert.butyloxycarbonyl)amino]-1-[2-(methoxycarbonyl)ethyl]-piperidine

6.45 g of methyl acrylate are added to 5.00 g of 4-[(tert.butyloxycarbonyl)amino]-piperidine in 20 ml methanol. The reaction mixture is stirred for 7.5 hours at 70°C. After the reaction has ended, the reaction mixture is concentrated by evaporation, leaving a white solid.

Yield: 7.09 g (99 % of theory),

melting point: 91-93 °C

Mass spectrum (ESI⁺): 287 [M+H]⁺

The following compounds are obtained analogously to Example V:

(1) *trans*-4-[(tert.butyloxycarbonyl)amino]-1-{N-[2-(methoxycarbonyl)ethyl]-N-methylamino}-cyclohexane

R_f value: 0.55 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): 315 [M+H]⁺

(2) 1-{1-[2-(ethoxycarbonyl)ethyl]-piperidin-4-yl}-4-(tert.butyloxycarbonyl)-piperazine

R_f value: 0.29 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 95:5:1)

Example VI*trans*-4-[(tert.butyloxycarbonyl)amino]-1-(methylamino)-cyclohexane

A suspension of 26.30 g of *trans*-4-[(tert.butyloxycarbonyl)amino]-1-[N-(trifluormethylcarbonyl)-N-methylamino]-cyclohexane in 250 ml methanol is heated to 50°C with stirring for a few minutes, until a clear solution is formed. Then 50 ml 2N sodium hydroxide solution are added with stirring. A slightly cloudy solution is formed which is stirred for a further 2.5

hours at ambient temperature. The reaction mixture is concentrated by evaporation, the residue is taken up in 2N citric acid solution and extracted with methylene chloride/methanol (9:1). Then it is made alkaline with 2N sodium hydroxide solution and extracted again with methylene chloride/methanol (9:1). The combined extracts are dried over magnesium sulphate and concentrated by evaporation.

Yield: 16.00 g (86 % of theory),

melting point: 120-122°C

Mass spectrum (ESI⁺): 229 [M+H]⁺

Example VII

trans-4-[(tert.butyloxycarbonyl)amino]-1-[N-(trifluormethylcarbonyl)-N-methylamino]-cyclohexane

4.54 g of sodium hydride at ambient temperature are added in batches with stirring to a suspension of 27.10 g of trans-4-[(tert.butyloxycarbonyl)amino]-1-[(trifluoromethylcarbonyl)amino]-cyclohexane in 220 ml of dimethylformamide. The slightly cloudy reaction solution is stirred for approx. a further 20 minutes at ambient temperature, then 6.47 ml of methyl iodide are added dropwise while cooling with an ice bath, whereupon a colourless precipitate slowly settles out. The reaction mixture is stirred overnight at ambient temperature and then poured onto 750 ml of ice-cold water for working up and neutralised with citric acid. The precipitate formed is filtered off, washed with water and dried in the desiccator.

Yield: 26.40 g (93 % of theory),

melting point: 158-166°C

R_f value: 0.75 (silica gel, methylene chloride/methanol = 95:5)

Example VIII

trans-4-[(tert.butyloxycarbonyl)amino]-1-[(trifluormethylcarbonyl)amino]-cyclohexane

10.56 ml of methyl trifluoroacetate are quickly added dropwise to 22.10 g of 1-amino-4-[(tert.butyloxycarbonyl)amino]-cyclohexane in 110 ml methanol whilst cooling with an ice bath, whereupon a white precipitate is formed. Then the ice bath is removed and the reaction mixture is stirred for a further 3.5 hours at ambient temperature. The precipitate formed is filtered off, washed with 50 ml ice-cold methanol and a little diethylether and dried in the desiccator.

Yield: 27.26 g (85 % of theory),

melting point: 245-246° (decomposition)

R_f value: 0.4 (silica gel, methylene chloride/methanol = 95:5)

Example IX

N-(3-aminopropyl)-sarcosine ethyl ester-hydrochloride

20 ml trifluoroacetic acid are added dropwise to a solution of 6.10 g of N-[3-(tert.butyloxycarbonylamino)-propyl]-sarcosine ethylester in 40 ml methylene chloride whilst cooling with an ice bath. The reaction mixture is then stirred for about another three hours at 0°C until the development of gas has ceased. For working up the solvent is substantially distilled off in vacuo using the rotary evaporator. The residue is taken up in ethereal hydrochloric acid solution and again concentrated to dryness by evaporation.

Yield: 4.72 g (86 % of theory)

R_f value: 0.80 (silica gel, acetonitrile/water/trifluoroacetic acid = 50:50:1)

Mass spectrum (EI): m/z = 174 [M]⁺

Example XN-[3-(tert.butyloxycarbonylamino)propyl]-sarcosine ethyl ester

A solution of 17.90 g of 3-(tert.butyloxycarbonylamino)propyl bromide in 50 ml acetonitrile is added dropwise, within 30 minutes, to a mixture of 11.55 g of sarcosine ethyl ester hydrochloride and 28.8 ml of Hünig's base in 200 ml acetonitrile whilst cooling with an ice bath. The reaction mixture is allowed to come back up to ambient temperature overnight in the ice bath. Then the solvent is distilled off using a rotary evaporator, the residue is taken up in tert-butyl-methylether and washed with ice-cold water. The organic phase is dried over magnesium sulphate and concentrated by evaporation. The crude product is chromatographed on a silica gel column with methylene chloride/methanol/concentrated aqueous ammonia solution (100:2:0.1).

Yield: 20.62 g (30 % of theory),

R_f value: 0.50 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 20:1:0.1)

Mass spectrum (ESI⁺): m/z = 275 [M+H]⁺

Example XI4-[(3-chloro-4-fluorophenyl)amino]-6-{4-[(tert.butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidin-1-yl}-pyrimido-[5,4-d]pyrimidine

1.03 g of 4-[(tert.butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidine are added to 676 mg of 4-[(3-chloro-4-fluorophenyl)amino]-6-methylsulphinyipyrimido[5,4-d]pyrimidine and 0.42 ml triethylamine in 10 ml dioxane and the reaction mixture is refluxed for one hour. The reaction solution is concentrated by evaporation and the residue taken up in methylene chloride. The solution is washed with dilute potassium carbonate solution and water, dried over magnesium sulphate and concentrated by evaporation. The crude product is

purified by chromatography over a silica gel column with methylene chloride/methanol (98:2).

Yield: 750 mg (71 % of theory),

melting point: 186-189°C (decomposition)

Mass spectrum (ESI⁺): m/z = 532, 534 [M+H]⁺

The following compounds are obtained analogously to Example XI:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-(N-{trans-4-[(tert.-butyloxycarbonyl)amino]-cyclohex-1-yl}-N-methylamino)-pyrimido[5,4-d]pyrimidine

melting point: 202.5-204.5°C

Mass spectrum (ESI⁺): m/z = 502, 504 [M+H]⁺

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-methylamino-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimine

R_f value: 0.30 (silica gel, toluene/dioxane/methanol/concentrated aqueous ammonia solution = 20:50:20:10)

Mass spectrum (ESI⁺): m/z = 416, 418 [M+H]⁺

(3) 4-[(3-bromophenyl)amino]-6-{[1-(tert.butyloxycarbonyl)-piperidin-4-yl]amino}-pyrimido[5,4-d]pyrimidine

melting point: 205°C

Mass spectrum (ESI⁺): m/z = 500, 502 [M+H]⁺

(3) 4-[(3-bromophenyl)amino]-6-{[1-(tert.butyloxycarbonyl)-piperidine-3-yl]amino}-pyrimido[5,4-d]pyrimidine

melting point: 218°C (decomposition)

Mass spectrum (EI): m/z = 499, 501 [M]⁺

Example XII4-[(tert.butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidine

2.44 g of 1-benzyl-4-[(tert.butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidine in 20 ml methanol are hydrogenated in the presence of 300 mg palladium (10% on activated charcoal) as catalyst at ambient temperature and at a hydrogen pressure of 50 psi for about 22 hours until the calculated amount of hydrogen is taken up. The catalyst is filtered off and the filtrate concentrated by evaporation.

Yield: 1.72 g (95 % of theory),

R_f value: 0.15 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): m/z = 259 [M+H]⁺

Example XIII1-benzyl-4-[(tert.butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidine

3.97 g of di-tert.butyl pyrocarbonate are added to a suspension of 5.05 g of 4-amino-1-benzyl-4-(methoxycarbonyl)-piperidine in 80 ml methylene chloride. Then 16 ml of 2N sodium hydroxide solution are added dropwise, with stirring, at ambient temperature, whereupon a precipitate is formed which is in the aqueous phase. After one hour the organic phase is separated off, dried over magnesium sulphate and concentrated by evaporation. Since the crude product mixture obtained still contains starting material, it is dissolved in 30 ml tetrahydrofuran, mixed with 1.50 g of di-tert.butyl pyrocarbonate and a spatula tip of 4-dimethylamino-pyridine and refluxed for three hours. The reaction mixture is concentrated by evaporation, leaving a brown resin which is reacted without any further purification.

Yield: 2.64 g (48 % of theory),

R_f value: 0.65 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (EI): $m/z = 348$ $[M]^+$

Example XIV

1-(tert.butyloxycarbonyl)-4-({N-[(methoxycarbonyl)methyl]-
N-methylamino}methyl)-piperidine

First, 11.0 g of sarcosine methylester hydrochloride are converted into the free base by treating with 10-15% potassium carbonate solution. This is then heated to 110°C together with 2.0 g of (1-tert.-butyloxycarbonyl)-4-[(methylsulphonyloxy)-methyl]-piperidine in a pressurised vessel for six hours at a pressure of 2 bar. Then the reaction mixture is rinsed out of the pressurised vessel with methanol and concentrated by evaporation. A brown oil is left which is stirred with a little water. The aqueous phase is separated off and the organic phase is diluted with methylene chloride, dried over sodium sulphate and freed from solvent using a rotary evaporator. The crude product obtained is reacted without any further purification.

Yield: 2.49 g of brownish oil

The following compounds are obtained analogously to Example XIV:

(1) 1-tert.butyloxycarbonyl-4-([2-(methoxycarbonyl)-piperidin-1-yl]methyl)-piperidine

R_f value: 0.86 (silica gel, petroleum ether/ethyl acetate/methanol = 10:10:1)

Mass spectrum (ESI⁺): $m/z = 341$ $[M+H]^+$

(2) 1-tert.butyloxycarbonyl-4-([2-(methoxycarbonyl)-pyrrolidin-1-yl]methyl)-piperidine

R_f value: 0.74 (silica gel, petroleum ether/ethyl acetate/methanol = 10:10:1)

Mass spectrum (ESI⁺): $m/z = 327$ $[M+H]^+$

(3) 1-tert.butyloxycarbonyl-4-({4-[(ethoxycarbonyl)methyl]-piperazin-1-yl)methyl}-piperidine

R_f value: 0.69 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 370 [M+H]⁺

Example XV

4-[(3-chloro-4-fluorophenyl)amino]-6-({trans-4-[(2-hydroxyethyl)amino]-cyclohex-1-yl)amino}-pyrimido[5,4-d]pyrimidine

0.23 ml of 2-bromoethanol and 0.61 ml of diisopropyl-ethylamine are added to 1.16 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-amino-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine in 8 ml acetonitrile at ambient temperature. The resulting mixture is refluxed. After about 5 hours another 0.05 ml of 2-bromoethanol are added and the mixture is heated for another eight hours to complete the reaction. The suspension is concentrated by evaporation, the residue is mixed with ice-cold water, made slightly alkaline with sodium hydroxide solution and suction filtered. The still moist filter residue is taken up in methylene chloride/methanol. The cloudy solution is washed with water, dried over magnesium sulphate and concentrated by evaporation. The yellow crude product is stirred with about 30 ml methanol, briefly heated to boiling, cooled slightly, suction filtered and washed with cold methanol. Yield: 990 mg (76 % of theory), melting point: 165-172°C

Mass spectrum (ESI⁺): m/z = 432, 434 [M+H]⁺

The following compound is obtained analogously to Example XV:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[(2-hydroxyethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.50 (silica gel, toluene/dioxane/methanol/concentrated aqueous ammonia solution = 20:50:20:3)

Mass spectrum (ESI⁺): m/z = 432, 434 [M+H]⁺

Example XVI

4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-amino-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimidine
3.0 ml trifluoroacetic acid are added dropwise to 2.10 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-{trans-4-[(tert.butyl-oxy-carbonyl)amino]-cyclohex-1-yl}-N-methylamino)-pyrimido-[5,4-d]pyrimidine in 30 ml methylene chloride. The reaction mixture is stirred for 1.5 hours at ambient temperature, left to stand overnight and concentrated by evaporation the next morning. The residue is taken up in methylene chloride/methanol (5:1), washed with 2N sodium hydroxide solution and water, dried over magnesium sulphate and concentrated by evaporation. The yellow crude product is triturated with diethyl ether, suction filtered and dried in vacuo.

Yield: 1.60 g (95 % of theory),

melting point: 203-205°C

Mass spectrum (ESI⁺): m/z = 402, 404 [M+H]⁺

The following compounds are obtained analogously to Example XVI:

(1) 4-[(3-bromophenyl)amino]-6-[(piperidin-4-yl)amino]-pyrimido[5,4-d]pyrimidine

melting point: 215°C

Mass spectrum (ESI⁺): m/z = 400, 402 [M+H]⁺

(2) 4-[(3-bromophenyl)amino]-6-[(piperidin-3-yl)amino]-pyrimido[5,4-d]pyrimidine

melting point: 178°C

Mass spectrum (ESI⁺): m/z = 400, 402 [M+H]⁺

Example XVII

4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-[(vinylsulphonyl)amino]-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine
0.38 ml of diisopropyl-ethylamine are added to 388 mg of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-amino-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine in 25 ml of tetrahydrofuran. The mixture is cooled to -55°C under a nitrogen atmosphere in a bath of acetone and dry ice. Then a solution of 0.13 ml chloroethanesulphonic acid chloride in 5 ml of tetrahydrofuran is added dropwise and stirred for a further 1.5 hours at -55°C. The reaction mixture is quenched with a mixture of 10 ml of 1N hydrochloric acid and 10 ml of saturated sodium chloride solution and mixed with some ethyl acetate. The organic phase is filtered through 8.5 g of Extrelut (E. Merck, Darmstadt) and eluted with 100 ml of methylene chloride/methanol (9:1). The filtrate is concentrated by evaporation, leaving a yellow solid.

Yield: 216 mg (45 % of theory),

melting point: 226-230°C (decomposition)

Mass spectrum (EI): m/z = 477, 479 [M]⁺

Example XVIII

(R)-4-[(1-phenylethyl)amino]-6-methylsulphinyl-pyrimido[5,4-d]pyrimidine and

(R)-4-[(1-phenylethyl)amino]-6-methylsulphonyl-pyrimido[5,4-d]pyrimidine

28.80 g of 3-chloroperbenzoic acid (content: 70 %) are added batchwise, with stirring, to 17.40 g of (R)-4-[(1-phenylethyl)amino]-6-methylthio-pyrimido[5,4-d]pyrimidine in 180 ml methylene chloride at ambient temperature. Then the reaction mixture is stirred for about an hour at ambient temperature. The white precipitate formed is filtered off and the filtrate is washed with sodium hydrogen carbonate solution, dried over magnesium sulphate and concentrated by evaporation. The oily

orange residue is a mixture of sulphone and sulphoxide (about 85:15 according to $^1\text{H-NMR}$).

R_f value: 0.47 (silica gel, cyclohexane/ethyl acetate/methanol = 5:4:1)

Mass spectrum (ESI^+): m/z = 352 $[\text{M}+\text{Na}]^+$ (sulphone), 336 $[\text{M}+\text{Na}]^+$ (sulphoxide)

Example XIX

(R)-4-[(1-phenylethyl)amino]-6-methylthio-pyrimido[5,4-d]-
pyrimidine

10.7 ml of diisopropyl-ethylamine and 9.4 ml of D(+)-1-phenyl-ethylamine are added to 13.00 g of 4-chloro-6-methylthio-pyrimido[5,4-d]pyrimidine in 100 ml of dimethylformamide. The mixture is stirred for four hours at ambient temperature. For working up the reaction mixture is poured onto 200 ml of water. The aqueous phase is extracted with methylene chloride, the combined organic phases are dried over magnesium sulphate and concentrated by evaporation. The dark brown oily residue is taken up in ethyl acetate and extracted with 10% citric acid. The organic phase is dried over magnesium sulphate and concentrated by evaporation, leaving a reddish-brown oil.

Yield: 17.40 g (96 % of theory),

R_f value: 0.63 (silica gel, cyclohexane/ethyl acetate/methanol = 5:4:1)

Mass spectrum (ESI^+): m/z = 298 $[\text{M}+\text{H}]^+$

Example XX

trans-1-[(tert.butyloxycarbonyl)amino]-4-[(2-hydroxy-2-methyl-prop-1-yl)amino]-cyclohexane

Prepared by reaction of trans-1-[(tert.butyloxycarbonyl)-amino]-4-amino-cyclohexane with 2,2-dimethyl-oxirane in ethanol using a closed vessel followed by chromatographic purification of the crude product mixture on silica gel.

R_f : 0.06 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI^+): m/z = 287 $[\text{M}+\text{H}]^+$

Preparation of the end products:

Example 1

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[1-(carboxymethyl)-piperidin-4-yl]amino}-pyrimido[5,4-d]pyrimidine

2.0 ml of 1N sodium hydroxide solution are added to a suspension of 400 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine in 5.0 ml tetrahydrofuran. The clear solution formed is stirred for approx. a further three hours at ambient temperature. Then the reaction solution is neutralised with 1N hydrochloric acid and concentrated by evaporation using a rotary evaporator until the product starts to crystallise out. The yellow precipitate is filtered off, washed with water and diethylether and dried in vacuo at 60°C.

Yield: 365 mg (96 % of theory),
melting point: 155°C (decomposition)
Mass spectrum (EI): m/z = 431, 433 [M]⁺

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[1-(2-carboxyethyl)-piperidin-4-yl]amino}-pyrimido[5,4-d]pyrimidine

melting point: 217-225°C
Mass spectrum (EI): m/z = 445, 447 [M]⁺

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[1-(3-carboxypropyl)-piperidin-4-yl]amino}-pyrimido[5,4-d]pyrimidine

melting point: 145-165°C
Mass spectrum (EI): m/z = 459, 461 [M]⁺

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({trans-4-[N-(carboxymethyl)-N-methylamino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 220-228°C

Mass spectrum (ESI⁺): m/z = 460, 462 [M+H]⁺

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({trans-4-[N-(2-carboxyethyl)-N-methylamino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 202-205°C

Mass spectrum (ESI⁺): m/z = 474, 476 [M+H]⁺

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({trans-4-[N-(3-carboxypropyl)-N-methylamino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 217-221°C

Mass spectrum (ESI⁺): m/z = 488, 490 [M+H]⁺

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(carboxymethyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine

melting point: 240°C (decomposition)

Mass spectrum (EI): m/z = 417, 419 [M]⁺

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-(2-carboxyethyl)-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine

melting point: 111-145°C

Mass spectrum (EI): m/z = 431, 433 [M]⁺

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{4-[1-(2-carboxyethyl)-piperidin-4-yl]-piperazin-1-yl}-pyrimido[5,4-d]pyrimidine

melting point: 213°C (decomposition)

Mass spectrum (EI): m/z = 514, 516 [M]⁺

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[1-(carboxymethyl)-piperidin-4-yl]ethylamino}-pyrimido[5,4-d]pyrimidine

melting point: 246-249°C (decomposition)

Mass spectrum (EI): m/z = 459, 461 [M]⁺

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(4-carboxypiperidin-1-yl)ethylamino]-pyrimido[5,4-d]pyrimidine

melting point: 190°C (decomposition)

Mass spectrum (EI): $m/z = 445, 447 [M]^+$

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-[N-(2-carboxy-ethyl)-N-methylamino]-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

melting point: 139-165°C (decomposition)

Mass spectrum (EI): $m/z = 459, 461 [M]^+$

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{3-[4-(2-carboxy-ethyl)-piperidin-1-yl]-pyrrolidin-1-yl}-pyrimido[5,4-d]pyrimidine

R_f value: 0.63 (silica gel, methylene chloride/methanol/triethylamine = 2:1:0.1)

Mass spectrum (EI): $m/z = 499, 501 [M]^+$

(13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(carboxymethyl)-piperazin-1-yl]ethylamino}-pyrimido[5,4-d]pyrimidine

melting point: 240-242°C (decomposition)

Mass spectrum: (ESI⁻): $m/z = 459, 461 [M-H]^-$

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-amino-4-carboxypiperidin-1-yl)-pyrimido[5,4-d]pyrimidine

melting point: 277-282°C

Mass spectrum (EI): $m/z = 417, 419 [M]^+$

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-(N-carboxymethyl-N-methylamino)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

R_f value: 0.05 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁻): $m/z = 444, 446 [M-H]^-$

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[(2-carboxyethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

melting point: 209-214°C

Mass spectrum (ESI⁻): $m/z = 458, 460 [M-H]^-$

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[(carboxymethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine
melting point: 226-235°C

Mass spectrum (ESI⁻): m/z = 444, 446 [M-H]⁻

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-({trans-4-[N,N-bis-(carboxymethyl)amino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]-pyrimidine

melting point: 245°C (decomposition)

Mass spectrum (ESI⁻): m/z = 502, 504 [M-H]⁻

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[N,N-bis(2-carboxyethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

melting point: 160-169°C

Mass spectrum (ESI⁻): m/z = 530, 532 [M-H]⁻

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-(3-{[N,N-bis(2-carboxyethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.79 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 90:10:1)

Mass spectrum (ESI⁻): m/z = 530, 532 [M-H]⁻

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[N,N-bis(carboxymethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.85 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 90:10:1)

Mass spectrum (ESI⁻): m/z = 502, 504 [M-H]⁻

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-(N-{trans-4-[N',N']-bis(carboxymethyl)amino]-cyclohex-1-yl}-N-methylamino)-pyrimido[5,4-d]pyrimidine

R_f value: 0.33 (Reversed phase ready-made TLC plate (E. Merck), methanol/5% aqueous sodium chloride solution = 8:2)

Mass spectrum (ESI⁻): m/z = 516, 518 [M-H]⁻

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-(N-{trans-4-[(carboxymethyl)amino]-cyclohex-1-yl}-N-methylamino)-pyrimido[5,4-d]pyrimidine

R_f value: 0.30 (Reversed phase ready-made TLC plate (E. Merck), methanol/5% aqueous sodium chloride solution = 8:2)

Mass spectrum (ESI⁻): m/z = 558, 560 [M-H]⁻

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-(3-{[(2-carboxyethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine
melting point: 173-179°C

Mass spectrum (ESI⁻): m/z = 558, 560 [M-H]⁻

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-(3-{[N,N-bis(carboxymethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.82 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 90:10:1)

Mass spectrum (ESI⁻): m/z = 502, 504 [M-H]⁻

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-(3-{[(carboxymethyl)amino]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.82 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 90:10:1)

Mass spectrum (ESI⁻): m/z = 444, 446 [M-H]⁻

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-({trans-4-[(carboxymethyl)amino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]pyrimidine
melting point: 201-205°C (decomposition)

Mass spectrum (ESI⁻): m/z = 444, 446 [M-H]⁻

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-(N-{trans-4-[N'-(carboxymethyl)-N'-methylamino]-cyclohex-1-yl}-N-methylamino)-pyrimido[5,4-d]pyrimidine

melting point: 200°C (decomposition)

Mass spectrum (ESI⁻): m/z = 472, 474 [M-H]⁻

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-[(2-carboxy-piperidin-1-yl)methyl]-piperidine-1-yl}-pyrimido[5,4-d]pyrimidine
(carried out with potassium tert.butoxide as base)

melting point: 225-237°C (decomposition)

Mass spectrum (ESI⁻): m/z = 498, 500 [M-H]⁻

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-methyl-4-[(2-carboxyethyl)amino]-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine
melting point: 157-160°C

Mass spectrum (ESI⁻): m/z = 458, 460 [M-H]⁻

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[4-(carboxymethyl)-piperazin-1-yl]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.60 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 90:10:1)

Mass spectrum (ESI⁻): m/z = 513, 515 [M-H]⁻

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-methyl-4-[(carboxymethyl)amino]-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine
melting point: 160°C (decomposition)

Mass spectrum (ESI⁻): m/z = 444, 446 [M-H]⁻

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-[(2-carboxy-pyrrolidin-1-yl)methyl]-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine
(carried out with potassium tert.butoxide as base)

melting point: 140-162°C (decomposition)

Mass spectrum (ESI⁻): m/z = 484, 486 [M-H]⁻

Example 2

4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

778 mg of 4-amino-1-[(ethoxycarbonyl)methyl]-piperidine-dihydrochloride are added to 676 mg of a mixture of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-methylsulphonyl-pyrimido[5,4-d]pyrimidine and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-methyl-

sulphonyl-pyrimido[5,4-d]pyrimidine in 14 ml dioxane and 2 ml ethanol. Then 0.55 ml of triethylamine and 829 mg of potassium carbonate are added and the reaction mixture is refluxed for about seven hours. Then the reaction mixture is concentrated by evaporation and the residue is stirred with ice-cold water, suction filtered, washed with water and dried. The brownish-yellow crude product is purified by chromatography on a silica gel column with methylene chloride/ethanol (95:5).

Yield: 526 mg (57 % of theory),

melting point: 136-38°C

Mass spectrum (EI): m/z = 459, 461 [M]⁺

The following compounds are obtained analogously to Example 2:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 162-164°C

Mass spectrum (EI): m/z = 445, 447 [M]⁺

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(propyloxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 135-137°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(3) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(isopropyloxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 175-177°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(cyclohexyloxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 184-186°C

Mass spectrum (EI): m/z = 513, 515 [M]⁺

(5) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine
melting point: 136-137°C

Mass spectrum (ESI⁺): m/z = 460, 462 [M+H]⁺

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[3-(methoxycarbonyl)propyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine
melting point: 135-137°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{N-[(methoxycarbonyl)methyl]-N-methylamino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine
melting point: 131-134°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{N-[2-(methoxycarbonyl)ethyl]-N-methylamino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine
melting point: 126-128°C

Mass spectrum (EI): m/z = 487, 489 [M]⁺

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{N-[3-(methoxycarbonyl)propyl]-N-methylamino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine
melting point: 99-102°C

Mass spectrum (ESI⁺): m/z = 502, 504 [M+H]⁺

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-[(ethoxycarbonyl)methyl]-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine
melting point: 179-182°C

Mass spectrum (EI): m/z = 445, 447 [M]⁺

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-[2-(methoxycarbonyl)ethyl]-piperazin-1-yl]-pyrimido[5,4-d]pyrimidine
melting point: 140-142°C

Mass spectrum (EI): m/z = 445, 447 [M]⁺

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-{1-[2-(ethoxycarbonyl)ethyl]-piperidin-4-yl}-piperazin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.51 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (EI): m/z = 542, 544 [M]⁺

(13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]-pyrimidine

melting point: 128-130°C

Mass spectrum (EI): m/z = 487, 489 [M]⁺

(14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(ethoxycarbonyl)-piperidin-1-yl]ethylamino}-pyrimido[5,4-d]pyrimidine

melting point: 137-139°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(4-{N-[2-(methoxycarbonyl)ethyl]-N-methylamino}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.15 (silica gel, petroleum ether/ethyl acetate/methanol = 5:5:1)

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(16) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(3-{4-[2-(methoxycarbonyl)ethyl]-piperidin-1-yl}-pyrrolidin-1-yl)-pyrimido[5,4-d]pyrimidine

melting point: 166-168°C

Mass spectrum (EI): m/z = 513, 515 [M]⁺

(17) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 144°C

Mass spectrum (ESI⁺): m/z = 472, 474 [M+H]⁺

(18) 4-[(3-bromophenyl)amino]-6-(3-{N-[(methoxycarbonyl)methyl]-N-methylamino}propylamino)-pyrimido[5,4-d]pyrimidine
 R_f value: 0.35 (silica gel, cyclohexane/ethyl acetate/methanol = 5:4:1)

Mass spectrum (ESI⁺): m/z = 474, 476 [M+H]⁺

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

R_f value: 0.88 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[2-(methoxycarbonyl)-piperidin-1-yl]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

R_f value: 0.73 (silica gel, petroleum ether/ethyl acetate/methanol = 10:10:1)

Mass spectrum (ESI⁺): m/z = 514, 516 [M+H]⁺

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{[2-(methoxycarbonyl)-pyrrolidin-1-yl]methyl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

melting point: 151-154°C

Mass spectrum (ESI⁺): m/z = 500, 502 [M+H]⁺

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

melting point: 145-149°C

Mass spectrum (ESI⁺): m/z = 543, 545 [M+H]⁺

(23) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 129°C

Mass spectrum (EI): m/z = 427, 429 [M]⁺

(24) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 164°C

Mass spectrum (EI): $m/z = 407$ [M]⁺

(25) (R)-4-[(1-phenylethyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

R_f value: 0.39 (silica gel, ethyl acetate/methanol = 95:5)

Mass spectrum (EI): $m/z = 421$ [M]⁺

(26) 4-[(4-amino-3,5-dichlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 218°C

Mass spectrum (EI): $m/z = 476, 478, 480$ [M]⁺

(27) 4-[(4-amino-3,5-dibromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 167°C

Mass spectrum (EI): $m/z = 564, 566, 568$ [M]⁺

(28) 4-[(indol-5-yl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

melting point: 167°C

Mass spectrum (EI): $m/z = 432$ [M]⁺

(29) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({[trans-4-(6,6-dimethyl-2-oxo-morpholin-4-yl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

R_f value: 0.66 (silica gel, ethyl acetate)

Mass spectrum (ESI⁻): $m/z = 498, 500$ [M-H]⁻

Example 3

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

2.08 ml of triethylamine and 0.61 ml of ethyl bromoacetate are added to 2.01 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-

(piperazin-1-yl)ethylamino]-pyrimido[5,4-d]pyrimidine in 50 ml pyridine. The reaction mixture is stirred for two hours at ambient temperature. Then the reaction mixture is concentrated by evaporation, water is added and the mixture is extracted with methylene chloride. The combined organic phases are dried over magnesium sulphate and concentrated by evaporation. The yellow crude product is purified by chromatography on an aluminium oxide column (activity III) with methylene chloride/ethanol (99:1).

Yield: 1.97 g (81 % of theory),

melting point: 128-129°C

Mass spectrum (ESI⁺): m/z = 489 [M+H]⁺

The following compounds are obtained analogously to Example 3:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-piperidin-1-yl)-pyrimido[5,4-d]-pyrimidine

R_f value: 0.63 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({[2-(methoxycarbonyl)-ethyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine (The reaction is carried out with methyl 3-bromopropionate)

R_f value: 0.57 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({[(methoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

R_f value: 0.66 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (EI): m/z = 459, 461 [M]⁺

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 155-157°C

Mass spectrum (EI): m/z = 559, 561 [M]⁺

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 181-184°C

Mass spectrum (ESI⁺): m/z = 532, 534 [M+H]⁺

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({[(ethoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.75 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({N,N-bis[(ethoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.65 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI⁺): m/z = 560, 562 [M+H]⁺

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-({N,N-bis[(methoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.81 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 532, 534 [M+H]⁺

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-({N,N-bis[(methoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido-[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.83 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 532, 534 [M+H]⁺

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-({[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino)-pyrimido-[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 141-143°C

Mass spectrum (EI): m/z = 459, 461 [M]⁺

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-({[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)-N-methylamino)-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 169.5-171.5°C

Mass spectrum (ESI⁺): m/z = 474, 476 [M+H]⁺

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-{N',N'-bis[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimidine (for method see Example 3(11))

melting point: 162-164°C

Mass spectrum (ESI⁺): m/z = 546, 548 [M+H]⁺

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-({[(methoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.76 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 460, 462 [M+H]⁺

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-{N'-[(methoxycarbonyl)methyl]-N'-methylamino}-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 137-139.5°C

Mass spectrum (ESI⁺): m/z = 488, 490 [M+H]⁺

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-methyl-4-[(methoxycarbonyl)methyl]amino-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

R_f value: 0.59 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (ESI⁺): m/z = 460, 462 [M+H]⁺

(16) 4-[(3-bromophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)-methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine (The reaction is carried out with dimethyl bromomalonate in acetonitrile in the presence of diisopropyl-ethylamine as the auxiliary base)

melting point: 158-160°C

Mass spectrum (ESI⁺): m/z = 530, 532 [M+H]⁺

(17) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile with diisopropyl-ethylamine as the auxiliary base)

melting point: 113°C

Mass spectrum (ESI⁺): m/z = 472, 474 [M+H]⁺

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine (The reaction is carried out with dimethyl bromomalonate in acetonitrile in the presence of diisopropyl-ethylamine as the auxiliary base)

melting point: 192-193°C

Mass spectrum (ESI⁺): m/z = 504, 506 [M+H]⁺

(19) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine
(The reaction is carried out in acetonitrile in the presence of diisopropylethylamine)

R_f: 0.49 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 446, 448 [M+H]⁺

(20) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(phenyloxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine
(The reaction is carried out with phenyl bromoacetate in acetonitrile in the presence of diisopropylethylamine)

Melting point: 166°C

Mass spectrum (ESI⁺): m/z = 508, 510 [M+H]⁺

(21) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(benzyloxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine
(The reaction is carried out with benzyl bromoacetate in acetonitrile in the presence of diisopropylethylamine.)

Melting point: 145°C

Mass spectrum (ESI⁻): m/z = 520, 522 [M-H]⁻

(22) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(indan-5-yl-oxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with indan-5-yl bromoacetate in acetonitrile in the presence of diisopropylethylamine.)

Melting point: 133°C

Mass spectrum (EI): m/z = 547, 549 [M]⁺

(23) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(tert.butyl-oxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with tert.butyl bromoacetate in acetonitrile in the presence of diisopropylethylamine.)

Melting point: 146°C

Mass spectrum (ESI⁺): m/z = 488, 490 [M+H]⁺

Example 4

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-{4-[(diethoxyphosphoryl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

A suspension of 500 mg of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(piperazin-1-yl)ethylamino]-pyrimido[5,4-d]pyrimidine in 15 ml dioxane is heated to 95-100°C with stirring until the solid is substantially dissolved. Then first of all 100 µl of 37% formaldehyde solution and 190 µl of diethylphosphite are added with heating. The reaction mixture is stirred for about 4 hours at 100°C. For working up the reaction mixture is concentrated by evaporation, the residue is stirred with a little ice-cold water and extracted with methylene chloride. The combined organic phases are dried over sodium sulphate and concentrated by evaporation. The brownish-yellow crude product is purified by chromatography on an aluminium oxide column (activity III) with methylene chloride/methanol (98.5:1.5). Yield: 250 mg (36 % of theory),

R_f value: 0.70 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 9:1:0.01)

Mass spectrum (ESI⁻): m/z = 551, 553 [M-H]⁻

The following compounds are obtained analogously to Example 4:

(1) 4-[(3-bromophenyl)amino]-6-({1-[(diethoxyphosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

R_f value: 0.36 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.5)

Mass spectrum (EI): m/z = 549, 551 [M]⁺

(2) 4-[(3-bromophenyl)amino]-6-[(1-{[(ethoxy)(methyl)phosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine (reaction with diethoxymethylphosphine in tetrahydrofuran)

R_f value: 0.25 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:1)

Mass spectrum (EI): m/z = 519, 521 [M]⁺

Example 5

4-[(3-chloro-4-fluorophenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

A suspension of 720 mg 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-[(tert-butyloxycarbonyl)amino]-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine in 10 ml methylene chloride is mixed with 2 ml trifluoroacetic acid with stirring. The solution formed with the release of gas is left to stand overnight and then evaporated to dryness. The residue is taken up in methylene chloride, washed with dilute potassium carbonate solution and water and dried over magnesium sulphate. The solvent is distilled off and the yellow resin remaining is stirred with a little methanol. The yellow precipitate is suction filtered, washed with a little cold methanol and dried in the desiccator.

Yield: 565 mg (97 % of theory),

melting point: 182-184°C

Mass spectrum (ESI⁺): m/z = 432, 434 [M+H]⁺

Example 6

4-[(3-chloro-4-fluorophenyl)amino]-6-[4-[(N,N-bis[2-(methoxycarbonyl)ethyl]amino)methyl]-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

0.73 ml methyl acrylate are added to 1.00 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-(4-aminomethyl-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine in 25 ml methanol. The reaction mixture is refluxed for four hours, then another 0.35 ml of methyl acrylate are added. After another five hours under reflux, the reaction is almost complete and the mixture is concentrated by evaporation. The orange-yellow crude product is purified by

chromatography on a silica gel column with petroleum ether/ethyl acetate/methanol (1:1:0.1) as eluant.

Yield: 1.02 g (71 % of theory),

melting point: 113-118°C

Mass spectrum (ESI⁺): m/z = 560, 562 [M+H]⁺

The following compounds are obtained analogously to Example 6:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-({N,N-bis[2-(methoxycarbonyl)ethyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

R_f value: 0.90 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 560, 562 [M+H]⁺

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-({[2-(methoxycarbonyl)ethyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine (Only 1.5 equivalents of methyl acrylate are used)

R_f value: 0.60 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 474, 476 [M+H]⁺

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-methyl-4-[2-(methoxycarbonyl)ethyl]amino-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine (Only 1.4 equivalents of methyl acrylate are used)

melting point: 134-135°C

Mass spectrum (ESI⁺): m/z = 474, 476 [M+H]⁺

(4) 4-[(3-bromophenyl)amino]-6-({1-[1,2-bis(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine (The reaction is carried out with dimethyl maleate in dioxane)

melting point: 193°C

Mass spectrum (ESI⁻): m/z = 542, 544 [M-H]⁻

(5) 4-[(3-bromophenyl)amino]-6-[(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)amino]-

pyrimido-[5,4-d]pyrimidine (The reaction is carried out with diethyl glutaconate in dioxane)

melting point: 132°C

Mass spectrum (ESI⁺): m/z = 586, 588 [M+H]⁺

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{[2-(methoxycarbonyl)-ethyl]amino}-cyclohex-1-yl)amino]-pyrimido-[5,4-d]pyrimidine

(The reaction is carried out with 1.3 equivalents of methyl acrylate)

Melting point: 142-144°C

Mass spectrum (EI): m/z = 473, 475 [M]⁺

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{[2-(benzyloxycarbonyl)-ethyl]amino}-cyclohex-1-yl)amino]-pyrimido-[5,4-d]pyrimidine

(The reaction is carried out with 1.3 equivalents of benzyl acrylate in acetonitrile)

Melting point: 182-184°C

Mass spectrum (ESI⁺): m/z = 550, 552 [M+H]⁺

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(methoxycarbonyl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.1 equivalents of methyl acrylate)

Melting point: 132°C

Mass spectrum (ESI⁺): m/z = 460, 462 [M+H]⁺

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(tert.butyl-oxycarbonyl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.03 equivalents of tert.butyl acrylate in acetonitrile.)

R_f: 0.52 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 502, 504 [M+H]⁺

(10) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(phenyl-oxy-carbonyl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.04 equivalents of phenyl acrylate in acetonitrile)

Melting point: 130°C

Mass spectrum (ESI⁺): m/z = 522, 524 [M+H]⁺

(11) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(benzyloxy-carbonyl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.0 equivalents of benzyl acrylate)

Melting point: 104°C

Mass spectrum (ESI⁺): m/z = 536, 538 [M+H]⁺

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{[2-(phenyloxycarbonyl)-ethyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.0 equivalents of phenyl acrylate in acetonitrile)

R_f: 0.20 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 536, 538 [M+H]⁺

(13) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{[2-(indan-5-yloxycarbonyl)-ethyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.09 equivalents of indan-5-yl acrylate in acetonitrile. Indan-5-yl acrylate is obtained by reaction of indan-5-ol with acryloyl chloride in the presence of triethylamine.)

R_f: 0.23 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 576, 578 [M+H]⁺

(14) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(indan-5-yl-oxy-carbonyl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.08 equivalents of indan-5-yl acrylate in acetonitrile)

R_f: 0.50 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 560, 562 [M-H]⁺

(15) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[2-(diethoxyphosphoryl)-ethyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(The reaction is carried out with 1.04 equivalents of vinylphosphonic acid diethyl ester in acetonitrile)

R_f: 0.46 (silica gel, ethyl acetate/methanol/concentrated aqueous ammonia = 90:10:2)

Mass spectrum (ESI⁺): m/z = 538, 540 [M+H]⁺

Example 7

4-[(3-chloro-4-fluorophenyl)amino]-6-({[trans-4-(2-oxo-morpholin-4-yl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

0.61 ml of diisopropyl-ethylamine and 0.39 ml of ethyl bromoacetate are added to 970 mg of 4-[(3-chloro-4-fluorophenyl)amino]-6-({trans-4-[(2-hydroxyethyl)amino]-cyclohex-1-yl}amino)-pyrimido[5,4-d]pyrimidine in 5 ml dimethylformamide at ambient temperature. The suspension is briefly heated to 50°C in a water bath until a clear solution is formed. Then the reaction mixture is stirred for a further three hours at ambient temperature. For working up the mixture is combined with ice-cold water. The phases are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with water and saturated sodium chloride solution, dried over magnesium sulphate and concentrated by evaporation. The crude product is purified by chromatography on a silica gel column with methylene chloride/methanol (98.5:1.5 to 97:3) as eluant. Product is obtained exclusively as a yellow crystalline solid.

Yield: 466 mg (44 % of theory),

melting point: 213-223°C

Mass spectrum (ESI⁺): m/z = 472, 474 [M+H]⁺

The following compounds are obtained analogously to Example 7:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{4-[(2-oxo-morpholin-4-yl)methyl]-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine (The reaction is carried out in acetonitrile as solvent, producing predominantly non-cyclised product which is cyclised to form the lactone by heating with a little p-toluenesulphonic acid in toluene)

melting point: 202-204°C

Mass spectrum (ESI⁺): m/z = 472, 474 [M+H]⁺

Example 8

4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{[(2-{N-[(methoxycarbonyl)methyl]-N-methylamino}-ethyl)sulphonyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

0.21 ml Diisopropyl-ethylamine and 176 mg of sarcosine methylester hydrochloride are added to 195 mg of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-[(vinylsulphonyl)amino]-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine in 10 ml methanol at ambient temperature. The reaction mixture is refluxed for about 25 hours. After the reaction has ended the mixture is concentrated by evaporation. Since the product is obviously partly in the form of the free acid the residue is again dissolved in methanol, cooled under a nitrogen atmosphere in a bath of acetone/dry ice and combined with 0.2 ml of thionyl chloride. After heating to ambient temperature the solvent is distilled off in vacuo, the residue is dissolved in methylene chloride/methanol, washed with dilute sodium carbonate solution, dried over magnesium sulphate and concentrated by evaporation. The brownish crude product is purified by chromatography on a silica gel column with methylene chloride/methanol (98:2).

Yield: 51 mg (22 % of theory),

melting point: 171-174°C

Mass spectrum (ESI⁺): m/z = 581, 583 [M+H]⁺

The following compounds are obtained analogously to Example 8:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-({[trans-4-({[2-(2-oxo-morpholin-4-yl)-ethyl]sulphonyl}amino)-cyclohex-1-yl]-amino})-pyrimido[5,4-d]pyrimidine (By reaction with ethyl (2-hydroxy-ethylamino)-acetate hydrochloride in ethanol with no subsequent re-esterification as described in Example 8)

R_f value: 0.39 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (EI): m/z = 578, 580 [M]⁺

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-({[(2-({(methoxycarbonyl)methyl}amino)-ethyl)sulfonyl]amino})-cyclohex-1-yl)amino)-pyrimido[5,4-d]pyrimidine

Melting point: 178-182°C

Mass spectrum (ESI⁺): m/z = 567, 569 [M+H]⁺

The following compounds may also be obtained analogously to the preceding Examples and other methods known from the literature:

(1) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(2) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(3) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(4) 4-[(3-trifluoromethylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(5) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(6) 4-[(4-amino-3,5-dibromo-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(7) 4-[(4-amino-3,5-dichlor-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(8) 4-[(indol-5-yl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(9) 4-[(3-bromophenyl)amino]-6-(N-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}-N-methylamino)-pyrimido[5,4-d]pyrimidine

(10) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(11) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(12) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(13) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(14) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(15) 4-[(3-chlorophenyl)amino]-6-({1-[1,2-bis(methoxycarbonyl)-ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(16) 4-[(3-chlorophenyl)amino]-6-[(1-{1-[(methoxycarbonyl)methyl]-2-(methoxycarbonyl)-ethyl}-piperidin-4-yl)amino]-pyrimido[5,4-d]pyrimidine

(17) 4-[(3-chlorophenyl)amino]-6-[(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)amino]-pyrimido[5,4-d]pyrimidine

(18) 4-[(3-chlorophenyl)amino]-6-({1-[1,2-bis(ethoxycarbonyl)-ethyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(19) 4-[(3-chlorophenyl)amino]-6-({1-[(diethoxyphosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(20) 4-[(3-chlorophenyl)amino]-6-({1-[(dimethoxyphosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(21) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxy)(methyl)phosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(22) 4-[(3-chlorophenyl)amino]-6-({1-[(ethoxy)(methyl)phosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(23) 4-[(3-chlorophenyl)amino]-6-({1-[(hexyloxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(24) 4-[(3-chlorophenyl)amino]-6-(2-{N-[(methoxycarbonyl)methyl]-N-methylamino}ethylamino)-pyrimido[5,4-d]pyrimidine

(25) 4-[(3-chlorophenyl)amino]-6-(3-{N-[(methoxycarbonyl)methyl]-N-methylamino}propylamino)-pyrimido[5,4-d]pyrimidine

(26) 4-[(3-chlorophenyl)amino]-6-(4-{N-[(methoxycarbonyl)methyl]-N-methylamino}butylamino)-pyrimido[5,4-d]pyrimidine

(27) 4-[(3-chlorophenyl)amino]-6-(3-{N,N-bis[(methoxycarbonyl)methyl]amino}propylamino)-pyrimido[5,4-d]pyrimidine

(28) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(29) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(30) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(31) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine

(32) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-azepan-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(33) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-azepan-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(34) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-azepan-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(35) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-azepan-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(36) 4-[(3-chlorophenyl)amino]-6-(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(37) 4-[(3-chlorophenyl)amino]-6-(4-{N-[(methoxycarbonyl)methyl]-N-methylamino}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(38) 4-[(3-chlorophenyl)amino]-6-(4-[(methoxycarbonyl)methyl]-amino-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(39) 4-[(3-chlorophenyl)amino]-6-(4-{N,N-bis[(methoxycarbonyl)methyl]amino}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(40) 4-[(3-chlorophenyl)amino]-6-(4-{N-[(dimethoxyphosphoryl)methyl]-N-methylamino}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(41) 4-[(3-chlorophenyl)amino]-6-[4-(N-{[(ethoxy)(methyl)phosphoryl]methyl}-N-methylamino)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(42) 4-[(3-chlorophenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(43) 4-[(3-bromophenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(44) 4-[(3-methylphenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(45) 4-[(3-ethynylphenyl)amino]-6-[4-({N-[(methoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(46) 4-[(3-chlorophenyl)amino]-6-[4-({N-[(ethoxycarbonyl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(47) 4-[(3-chlorophenyl)amino]-6-[4-({[(ethoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(48) 4-[(3-chlorophenyl)amino]-6-[4-({N,N-bis[(ethoxycarbonyl)methyl]amino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(49) 4-[(3-chlorophenyl)amino]-6-[4-({N-[(dimethoxyphosphoryl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(50) 4-[(3-chlorophenyl)amino]-6-[4-({N-[(diethoxyphosphoryl)methyl]-N-methylamino}methyl)-piperidin-1-yl]-pyrimido[5,4-d]-pyrimidine

(51) 4-[(3-chlorophenyl)amino]-6-[4-(N-{[(ethoxy)(methyl)phosphoryl]methyl}-N-methylamino)methyl]-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(52) 4-[(3-chlorophenyl)amino]-6-(2-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(53) 4-[(3-bromophenyl)amino]-6-(2-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(54) 4-[(3-methylphenyl)amino]-6-(2-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(55) 4-[(3-ethynylphenyl)amino]-6-(2-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(56) 4-[(3-chlorophenyl)amino]-6-(2-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(57) 4-[(3-bromophenyl)amino]-6-(2-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(58) 4-[(3-ethynylphenyl)amino]-6-(2-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(59) 4-[(3-methylphenyl)amino]-6-(2-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(60) 4-[(3-chlorophenyl)amino]-6-(2-{4-[(dimethoxyphosphoryl)methyl]-piperazin-1-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(61) 4-[(3-chlorophenyl)amino]-6-(2-{1-[(dimethoxyphosphoryl)methyl]-piperidin-4-yl}ethylamino)-pyrimido[5,4-d]pyrimidine

(62) 4-[(3-chlorophenyl)amino]-6-[2-(4-{[(ethoxy)(methyl)phosphoryl]methyl}-piperazin-1-yl)ethylamino]-pyrimido[5,4-d]pyrimidine

(63) 4-[(3-chlorophenyl) amino]-6-[2-(1-[[ethoxy] (methyl) phosphoryl]methyl)-piperidin-4-yl]ethylamino)-pyrimido[5,4-d]-pyrimidine

(64) 4-[(3-chlorophenyl) amino]-6-(3-{1-[(methoxycarbonyl) methyl]-piperidin-4-yl}propylamino)-pyrimido[5,4-d]pyrimidine

(65) 4-[(3-chlorophenyl) amino]-6-(3-{4-[(methoxycarbonyl) methyl]-piperazin-1-yl}propylamino)-pyrimido[5,4-d]pyrimidine

(66) 4-[(3-bromophenyl) amino]-6-(3-{4-[(methoxycarbonyl) methyl]-piperazin-1-yl}propylamino)-pyrimido[5,4-d]pyrimidine

(67) 4-[(3-methylphenyl) amino]-6-(3-{4-[(methoxycarbonyl) methyl]-piperazin-1-yl}propylamino)-pyrimido[5,4-d]pyrimidine

(68) 4-[(3-ethynylphenyl) amino]-6-(3-{4-[(methoxycarbonyl) methyl]-piperazin-1-yl}propylamino)-pyrimido[5,4-d]pyrimidine

(69) 4-[(3-chloro-4-fluoro-phenyl) amino]-6-(3-{4-[(methoxycarbonyl) methyl]-piperazin-1-yl}propylamino)-pyrimido[5,4-d]-pyrimidine

(70) 4-[(3-chlorophenyl) amino]-6-({1-[(ethoxycarbonyl) methyl]-piperidin-4-yl}methylamino)-pyrimido[5,4-d]pyrimidine

(71) 4-[(3-bromophenyl) amino]-6-({1-[(ethoxycarbonyl) methyl]-piperidin-4-yl}methylamino)-pyrimido[5,4-d]pyrimidine

(72) 4-[(3-methylphenyl) amino]-6-({1-[(ethoxycarbonyl) methyl]-piperidin-4-yl}methylamino)-pyrimido[5,4-d]pyrimidine

(73) 4-[(3-ethynylphenyl) amino]-6-({1-[(ethoxycarbonyl) methyl]-piperidin-4-yl}methylamino)-pyrimido[5,4-d]pyrimidine

(74) 4-[(3-chlorophenyl)amino]-6-{[4-({N-[(ethoxycarbonyl)methyl]-N-methylamino)methyl}-cyclohex-1-yl)methylamino]-pyrimido[5,4-d]pyrimidine

(75) 4-[(3-chlorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-cyclohex-1-yl)methylamino]-pyrimido[5,4-d]pyrimidine

(76) 4-[(3-chlorophenyl)amino]-6-[(4-{[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(77) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(78) 4-[(3-methylphenyl)amino]-6-[(4-{[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(79) 4-[(3-bromophenyl)amino]-6-[(4-{[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(80) 4-[3-(ethynylphenyl)amino]-6-[(4-{[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine

(81) 4-[(3-chlorophenyl)amino]-6-{[4-({N-[(ethoxycarbonyl)methyl]-N-methylamino)methyl}-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

(82) 4-[(3-chlorophenyl)amino]-6-({4-[(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyl)aminocarbonyl]-cyclohex-1-yl}-amino)-pyrimido[5,4-d]pyrimidine

(83) 4-[(3-chlorophenyl)amino]-6-{[4-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}aminocarbonyl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

(84) 4-[(3-chlorophenyl)amino]-6-{[4-({4-[(methoxycarbonyl)methyl]-piperazin-1-yl}carbonyl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

(85) 4-[(3-chlorophenyl)amino]-6-[4-(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethyl)-piperazin-1-yl]-pyrimido[5,4-d]-pyrimidine

(86) 4-[(3-chlorophenyl)amino]-6-(4-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}-piperidin-1-yl)-pyrimido[5,4-d]pyrimidine

(87) 4-[(3-chlorophenyl)amino]-6-{7-[(methoxycarbonyl)methyl]-2,7-diaza-spiro[4.4]non-2-yl}-pyrimido[5,4-d]pyrimidine

(88) 4-[(3-chlorophenyl)amino]-6-[(1-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}-piperidin-4-yl)amino]-pyrimido[5,4-d]-pyrimidine

(89) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,4-d]pyrimidine

(90) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,4-d]pyrimidine

(91) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,4-d]pyrimidine

(92) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,4-d]pyrimidine

(93) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,4-d]pyrimidine

(94) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,2-d]pyrimidine

(95) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,2-d]pyrimidine

(96) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,2-d]pyrimidine

(97) 4-[(3-ethynylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[3,2-d]pyrimidine

(98) 4-[(3-chlorophenyl)amino]-7-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[4,3-d]pyrimidine

(99) 4-[(3-chlorophenyl)amino]-7-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[4,5-d]pyrimidine

(100) 4-[(3-chlorophenyl)amino]-7-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrido[2,3-d]pyrimidine

(101) 4-[(3-chlorophenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(102) 4-[(3-bromophenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(103) 4-[(3-methylphenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(104) 4-[(3-ethynylphenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(105) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[4-amino-4-(methoxycarbonyl)-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(106) 4-[(1-phenylethyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(107) 4-[(3-chlorophenyl)amino]-6-{[4-(2-oxo-morpholin-4-yl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

(108) 4-[(3-chlorophenyl)amino]-6-{4-[(2-oxo-morpholin-4-yl)-methyl]-piperidin-1-yl}-pyrimido[5,4-d]pyrimidine

(109) 4-[(3-chlorophenyl)amino]-6-{[2-(2-oxo-morpholin-4-yl)-ethyl]amino}-pyrimido[5,4-d]pyrimidine

Example 9

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	<u>1.5 mg</u>
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 10Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	<u>2.0 mg</u>
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facettted on both sides and notched on one side.

Example 11Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	50.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg

colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	<u>1.0 mg</u>
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 12

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		50.0 mg
corn starch (dried)	approx.	80.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		<u>3.0 mg</u>
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 13Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	<u>840.0 mg</u>
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 14Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water	ad 100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt

of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 15

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 16

Ampoules containing 50 mg of active substance

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Example 17Capsules for powder inhalation containing 5 mg of active substance

1 capsule contains:

active substance	5.0 mg
lactose for inhalation	<u>15.0 mg</u>
	20.0 mg

Preparation:

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg).

weight of capsule: 70.0 mg

size of capsule = 3

Example 18Solution for inhalation for hand-held nebulisers containing 2.5 mg active substance

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	
ethanol/water (50/50)	ad 15.000 mg

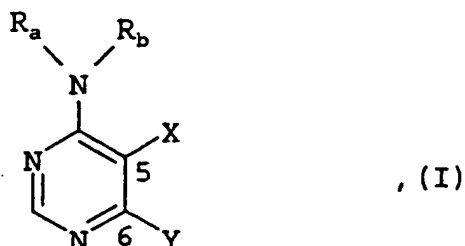
Preparation:

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

Patent Claims

1. Bicyclic heterocycles of general formula



wherein

R_a denotes a hydrogen atom or a C_{1-4} -alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4} -alkyl, hydroxy, C_{1-4} -alkoxy, C_{3-6} -cycloalkyl, C_{4-6} -cycloalkoxy, C_{2-5} -alkenyl or C_{2-5} -alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5} -alkenyloxy or C_{3-5} -alkynyloxy group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C_{1-4} -alkylsulphenyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkylsulphonyl, C_{1-4} -alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1-4} -alkyl groups, whilst the substituents may be identical or different,

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-CH=CH-CH=CH-$, $-CH=CH-NH$ or $-CH=N-NH$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4} -alkyl, trifluoromethyl or C_{1-4} -alkoxy group,

X and Y together denote a

$-N=C(-A-B)-CH=CH-$,
 $-CH=N-C(-A-B)=CH-$,
 $-CH=C(-A-B)-N=CH-$,
 $-CH=CH-C(-A-B)=N-$,
 $-N=C(-A-B)-N=CH-$ or
 $-CH=N-C(-A-B)=N-$ bridge, wherein

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $-O-C_{1-8}$ -alkylene, $-O-C_{4-7}$ -cycloalkylene, $-O-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene, $-O-C_{4-7}$ -cycloalkylene- C_{1-3} -alkylene or $-O-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene- C_{1-3} -alkylene group, whilst the oxygen atom of the abovementioned group in each case is linked to the bicyclic heteroaromatic ring,

an $-NR_4-C_{1-8}$ -alkylene, $-NR_4-C_{3-7}$ -cycloalkylene, $-NR_4-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene, $-NR_4-C_{3-7}$ -cycloalkylene- C_{1-3} -alkylene

or $-NR_4-C_{1,3}$ -alkylene- $C_{3,7}$ -cycloalkylene- $C_{1,3}$ -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a $C_{1,4}$ -alkyl group,

an oxygen atom which is linked to a carbon atom of the group B,

an $-NR_4-C_{4,7}$ -cycloalkylene-NH-SO₂- $C_{1,4}$ -alkylene or $-NR_4-C_{4,7}$ -cycloalkylene-N($C_{1,4}$ -alkyl)-SO₂- $C_{1,4}$ -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and R_4 is as hereinbefore defined,

an $-NR_4$ group, where the latter is linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

an azetidinylene, pyrrolidinylene, piperidinylene or hexahydroazepinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an azetidinylene- $C_{1,3}$ -alkylene, pyrrolidinylene- $C_{1,3}$ -alkylene, piperidinylene- $C_{1,3}$ -alkylene or hexahydroazepinylene- $C_{1,3}$ -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene or 1,4-homopiperazinylene group, these groups each being linked to a carbon atom of the group B,

a 1,4-piperazinylene- $C_{1,3}$ -alkylene or 1,4-homopiperazinylene- $C_{1,3}$ -alkylene group, whilst in each case the cyclic

nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -azetidinylene, $-NR_4$ -pyrrolidinylene, $-NR_4$ -piperidinylene or $-NR_4$ -hexahydroazepinylene group, whilst the $-NR_4$ - moiety of the abovementioned groups is linked in each case to the bicyclic heteroaromatic ring and in each case the cyclic nitrogen atom of the abovementioned groups is linked to a carbon atom of the group B,

an $-NR_4$ -azetidinylene- $C_{1,3}$ -alkylene, $-NR_4$ -pyrrolidinylene- $C_{1,3}$ -alkylene, $-NR_4$ -piperidinylene- $C_{1,3}$ -alkylene or $-NR_4$ -hexahydroazepinylene- $C_{1,3}$ -alkylene group, whilst in each case the $-NR_4$ - moiety of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned groups is in each case linked to the alkylene moiety,

an $-NR_4$ - $C_{3,7}$ -cycloalkylenecarbonyl group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

an $-NR_4$ - $C_{3,7}$ -cycloalkylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety, which may additionally be substituted by a $C_{1,4}$ -alkyl group, is linked to a carbon atom of the group B,

an $-NR_4$ - $C_{3,7}$ -cycloalkylenecarbonylamino- $C_{1,3}$ -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety may additionally be substituted by a $C_{1,4}$ -alkyl group,

an azetidinylenecarbonyl, pyrrolidinylencarbonyl, piperidinylencarbonyl or hexahydroazepinylenecarbonyl group,

whilst in each case the cyclic nitrogen atom of the above-mentioned groups is linked to the bicyclic heteroaromatic ring and the carbonyl group in each case is linked to a nitrogen atom of the group B,

an azetidinylenecarbonylamino, pyrrolidinylencarbonylamino, piperidinylencarbonylamino or hexahydroazepinylenecarbonylamino group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety, which may additionally be substituted by a C_{1-4} -alkyl group, is linked to a carbon atom of the group B,

an azetidinylenecarbonylamino- C_{1-3} -alkylene, pyrrolidinylencarbonylamino- C_{1-3} -alkylene, piperidinylencarbonylamino- C_{1-3} -alkylene or hexahydroazepinylenecarbonylamino- C_{1-3} -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety may additionally be substituted by a C_{1-4} -alkyl group, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_8)$ -alkylene- NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst

R_5 denotes a hydrogen atom,

a C_{1-4} -alkyl group, which may be substituted by a hydroxy, C_{1-4} -alkoxy, R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_8)$, amino, C_{1-4} -alkylamino or di- $(C_{1-4}$ -alkyl)-amino group or by a 4 to 7-membered alkyleneimino group, whilst in the abovementioned 6 to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an

oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group,

a C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group,

R₆, R₇ and R₈, which may be identical or different, in each case denote a hydrogen atom,

a C₁₋₆-alkyl group which may be substituted by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group or by a 4 to 7-membered alkyleneimino group, whilst in the abovementioned 6 to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group,

a C₄₋₇-cycloalkyl group optionally substituted by one or two methyl groups,

a C₃₋₅-alkenyl or C₃₋₅-alkynyl group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C₃₋₇-cycloalkyl-C₁₋₄-alkyl, aryl, aryl-C₁₋₄-alkyl or R_cCO-O-(R_cCR_d) group, whilst

R_c and R_d, which may be identical or different, in each case denote a hydrogen atom or a C₁₋₄-alkyl group and

R_e denotes a C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₁₋₄-alkoxy or C₅₋₇-cycloalkoxy group,

and R_f denotes a C₁₋₄-alkyl, aryl or aryl-C₁₋₄-alkyl group,

a 4 to 7-membered alkyleneimino group which is substituted by an R_eO-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R_eO-CO-C₁₋₄-alkyl, bis-(R_eO-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or

(R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined and

R₁₀ denotes a hydrogen atom, a C₁₋₄-alkyl, formyl, C₁₋₄-alkylcarbonyl or C₁₋₄-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R₁₀, whilst the abovementioned 5 to 7-membered rings are each additionally substituted at a carbon atom by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₁₀ are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group A,

a C_{5-7} -cycloalkyl group which is substituted by an amino, C_{1-4} -alkylamino or di- $(C_{1-4}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a C_{5-7} -cycloalkyl group wherein a methylene group is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group and in each case two hydrogen atoms in the cycloalkyl moiety are replaced by a straight-chained alkylene bridge, this bridge containing 2 to 6 carbon atoms, if the two hydrogen atoms are located at the same carbon atom, or contains 1 to 5 carbon atoms if the two hydrogen atoms are located at adjacent carbon atoms, or contains 2 to 4 carbon atoms, if the two hydrogen atoms are located at carbon atoms which are separated by one atom, whilst R_6 to R_9 are as hereinbefore defined,

or A together with B denotes a 1-azetidiny1 group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C_{4-6} -alkylene bridge, whilst in each case a methylene group in the C_{4-6} -alkylene bridge is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group wherein R_6 to R_9 are as hereinbefore defined,

a 1-pyrrolidinyl, 1-piperidinyl or 1-azacyclohept-1-yl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C_{3-6} -alkylene bridge, whilst in each case a methylene group in the C_{3-6} -alkylene

bridge is replaced by an $R_6O-CO-C_{1-4}$ -alkyleneimino, [bis- $(R_6O-CO)-C_{1-4}$ -alkylene]imino, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyleneimino or $(R_7O-PO-R_9)-C_{1-4}$ -alkyleneimino group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidino, piperidino or hexahydroazepino group which are substituted in each case by an amino, C_{1-4} -alkylamino or di- $(C_{1-4}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

whilst by the aryl moieties mentioned in the definition of the abovementioned groups is meant a phenyl group which may in each case be monosubstituted by R_{11} , mono-, di- or trisubstituted by R_{12} or monosubstituted by R_{11} and additionally mono- or disubstituted by R_{12} , whilst the substituents may be identical or different and

R_{11} may denote a cyano, carboxy, C_{1-4} -alkoxycarbonyl, aminocarbonyl, C_{1-4} -alkylaminocarbonyl, di- $(C_{1-4}$ -alkyl)-aminocarbonyl, C_{1-4} -alkylsulphenyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkylsulphonyl, hydroxy, C_{1-4} -alkylsulphonyloxy, trifluoro-

methyloxy, nitro, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, C₁₋₄-alkylcarbonylamino, N-(C₁₋₄-alkyl)-C₁₋₄-alkylcarbonylamino, C₁₋₄-alkylsulphonylamino, N-(C₁₋₄-alkyl)-C₁₋₄-alkylsulphonylamino, aminosulphonyl, C₁₋₄-alkylamino-sulphonyl or di-(C₁₋₄-alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group, and

R₁₂ denotes a fluorine, chlorine, bromine or iodine atom, a C₁₋₄-alkyl, trifluoromethyl or C₁₋₄-alkoxy group or

two R₁₂ groups, if they are bound to adjacent carbon atoms, together denote a C₃₋₅-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, stereoisomers and salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R₁ to R₃, whilst

R₁ and R₂, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, ethynyl or amino group,

a phenyl, phenoxy, benzyl or benzyloxy group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-\text{CH}=\text{CH}-\text{NH}$ or $-\text{CH}=\text{N}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote a

$-\text{N}=\text{C}(-\text{A}-\text{B})-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{CH}-$,
 $-\text{CH}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{C}(-\text{A}-\text{B})=\text{N}-$,
 $-\text{N}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$ or
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{N}-$ bridge, whilst

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $-\text{NR}_4-\text{C}_{1-4}$ -alkylene, $-\text{NR}_4$ -cyclohexylene, $-\text{NR}_4$ -cyclohexylene- $\text{NH}-\text{SO}_2-\text{C}_{1-3}$ -alkylene, $-\text{NR}_4-\text{C}_{1-3}$ -alkylene-cyclohexylene, $-\text{NR}_4$ -cyclohexylene- C_{1-3} -alkylene or $-\text{NR}_4-\text{C}_{1-3}$ -alkylene-cyclohexylene- C_{1-3} -alkylene group, whilst the $-\text{NR}_4$ - moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and

R_4 denotes a hydrogen atom or a methyl group,

an $-\text{NR}_4$ group, the latter being linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

a pyrrolidinylene or piperidinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylene- $C_{1,3}$ -alkylene group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene or 1,4-homopiperazinylene group, these groups each being linked to a carbon atom of the group B,

a 1,4-piperazinylene- $C_{1,2}$ -alkylene or 1,4-homopiperazinylene- $C_{1,2}$ -alkylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -piperidinylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to a carbon atom of the group B,

an $-NR_4$ -piperidinylene- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to the alkylene moiety,

an $-NR_4$ -cyclohexylenecarbonyl group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring,

a piperidinylencarbonyl group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring and the carbonyl group is linked to a nitrogen atom of the group B,

a piperidinylencarbonylamino group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

a piperidinylencarbonylamino- C_{1-2} -alkylene group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst

R_5 denotes a hydrogen atom or

a C_{1-4} -alkyl group which may be substituted by an R_6O-CO group,

R_6 , R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8} -alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a 5-indanyl group or a benzyl group optio-

nally substituted in the phenyl moiety by one or two methyl groups and

R_9 denotes a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_{10} , which is additionally substituted in each case at a carbon atom by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a methyl, ethyl or $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

a C_{5-6} -cycloalkyl group which is substituted by an amino, C_{1-2} -alkylamino or di- $(C_{1-2}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

or A and B together denote a 1-pyrrolidinyl or 1-piperidinyl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C_{4-5} -alkylene bridge, whilst in each case a methylene group in the C_{4-5} -alkylene bridge is replaced by an $R_6O-CO-C_{1-4}$ -alkylene-imino group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted in each case by an amino, C_{1-2} -alkylamino or di- $(C_{1-2}$ -alkyl)-amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,
the tautomers, stereoisomers and salts thereof.

3. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, ethynyl or amino group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-\text{CH}=\text{CH}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote a

$-\text{N}=\text{C}(-\text{A}-\text{B})-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{CH}-$,
 $-\text{CH}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{C}(-\text{A}-\text{B})=\text{N}-$,
 $-\text{N}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$ or
 $-\text{CH}=\text{N}-\text{C}(-\text{A}-\text{B})=\text{N}-$ bridge, whilst

the left-hand end of these bridges is linked to position 5 and the right-hand end of these bridges is linked to position 6 of the pyrimidine ring,

A denotes an $-\text{NR}_4-\text{C}_{1..4}-$ alkylene, $-\text{NR}_4-$ cyclohexylene, $-\text{NR}_4-$ cyclohexylene- $\text{NH}-\text{SO}_2-\text{C}_{1..3}-$ alkylene, $-\text{NR}_4-$ methylene-cyclohexylene, $-\text{NR}_4-$ cyclohexylene-methylene or $-\text{NR}_4-$ methylene-cyclohexylene-methylene group, whilst the $-\text{NR}_4-$ moiety

of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a methyl group,

an $-NR_4$ group, the latter being linked to a carbon atom of the group B and R_4 is as hereinbefore defined,

a pyrrolidinylene or piperidinylene group optionally substituted by one or two methyl groups, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylene- $C_{1,2}$ -alkylene group, whilst the cyclic nitrogen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene group, this group being linked in each case to a carbon atom of the group B,

a 1,4-piperazinylene- $C_{1,2}$ -alkylene group, the cyclic nitrogen atom of the abovementioned group being linked to the bicyclic heteroaromatic ring,

an $-NR_4$ -piperidinylene group, whilst the $-NR_4$ - moiety of the abovementioned group is linked to the bicyclic heteroaromatic ring and the cyclic nitrogen atom of the abovementioned group is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring and the nitrogen atom of the carbonylamino moiety is linked to a carbon atom of the group B,

an $-NR_4$ -cyclohexylenecarbonylamino- $C_{1,2}$ -alkylene group, whilst the $-NR_4$ - moiety is linked to the bicyclic heteroaromatic ring, and

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety is straight-chained and contains 1 to 4 carbon atoms, whilst

R_5 denotes a hydrogen atom,

a C_{1-2} -alkyl group which may be substituted by an R_6O-CO group,

R_6 denotes a hydrogen atom,

a C_{1-8} -alkyl group,

a cyclopentyl, cyclohexyl, cyclopentylmethyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a 5-indanyl group or a benzyl group optionally substituted in the phenyl moiety by one or two methyl groups and

R_7 , R_8 and R_9 , which may be identical or different, in each case denote a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-3}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-3}$ -alkyl or $(R_7O-PO-R_9)-C_{1-3}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined, and

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis-

(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

or A and B together denote a 1-pyrrolidinyl or 1-piperidinyl group wherein the two hydrogen atoms of a methylene group are replaced by a straight-chained C₄₋₅-alkylene bridge, whilst in each case a methylene group in the C₄₋₅-alkylene bridge is replaced by an R₆O-CO-C_{1,2}-alkylene-imino group wherein R₆ is as hereinbefore defined,

a piperidino group which is substituted by an amino group and by an R₆O-CO group, whilst R₆ is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R₆O-CO-C_{1,4}-alkyl group wherein R₆ is as hereinbefore defined, or

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

the tautomers, stereoisomers and salts thereof.

4. Compounds of general formula I according to at least one of claims 1 to 3, characterised in that X and Y together denote an -N=C(-A-B)-N=CH- bridge,

the tautomers, stereoisomers and salts thereof.

5. Bicyclic heterocyclic compounds of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl or amino group

or R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote an $-\text{CH}=\text{CH}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

X and Y together denote an $-\text{N}=\text{C}(-\text{A}-\text{B})-\text{N}=\text{CH}-$ bridge, whilst

the left-hand end of this bridge is linked to position 5 and the right-hand end of this bridge is linked to position 6 of the pyrimidine ring,

A denotes an $-\text{NR}_4-\text{C}_{1,3}-$ alkylene, $-\text{NR}_4-$ cyclohexylene or $-\text{NR}_4-$ cyclohexylene- $\text{NH}-\text{SO}_2-$ ethylene group, whilst the $-\text{NR}_4-$ moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a methyl group,

an $-\text{NR}_4$ group, the latter being linked to a carbon atom of the group B and R_4 being as hereinbefore defined,

an optionally methyl-substituted pyrrolidinylene or piperidinylene group, whilst in each case the cyclic nitrogen atom of the abovementioned groups is linked to the bicyclic heteroaromatic ring,

a piperidinylenemethylene group, whilst the cyclic nitrogen atom is linked to the bicyclic heteroaromatic ring,

a 1,4-piperazinylene group, this group being linked to a carbon atom of the group B, and

B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety is straight-chained and contains 1 to 4 carbon atoms, whilst

R_5 denotes a hydrogen atom,

a C_{1-2} -alkyl group which may be substituted by an R_6O-CO group,

R_6 denotes a hydrogen atom,

a C_{1-4} -alkyl, cyclohexyl, phenyl, benzyl or 5-indanyl group,

a pyrrolidino or piperidino group which is substituted in each case by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO -methyl or $(R_7O-PO-OR_8)$ -methyl group wherein R_6 is as hereinbefore defined and

R_7 and R_8 in each case denotes a methyl or ethyl group,

a piperidinyll group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl, $(R_7O-PO-OR_8)$ -ethyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 to R_9 are as hereinbefore defined and

R_9 denotes a methyl or ethyl group,

a 2-oxo-morpholino group, which may be substituted by one or two methyl groups,

or A and B together denote a piperidino group which is substituted by an amino group and by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1,2}$ -alkyl group, wherein R_6 is as hereinbefore defined,

the tautomers, stereoisomers and salts thereof.

6. The following compounds of general formula I according to claim 1:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(trans-4-{N-[(methoxycarbonyl)methyl]-N-methylamino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-[4-{N-[(methoxycarbonyl)methyl]-N-methylamino}methyl]-piperidin-1-yl]-pyrimido[5,4-d]pyrimidine

(4) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(5) 4-[(3-chlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine

(6) 4-[(3-methylphenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(7) 4-[(4-amino-3,5-dichlorophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(8) 4-[(4-amino-3,5-dibromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(9) 4-[(indol-5-yl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(ethoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{N,N-bis-[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(trans-4-{[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)amino]-pyrimido[5,4-d]pyrimidine,

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-[N-(trans-4-{N',N'-bis[(methoxycarbonyl)methyl]amino}-cyclohex-1-yl)-N-methylamino]-pyrimido[5,4-d]pyrimidine,

(14) 4-[(3-bromophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine,

(15) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-3-yl}amino)-pyrimido[5,4-d]pyrimidine,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-(1-[1,1-bis(methoxycarbonyl)methyl]-piperidin-4-yl)amino)-pyrimido[5,4-d]pyrimidine,

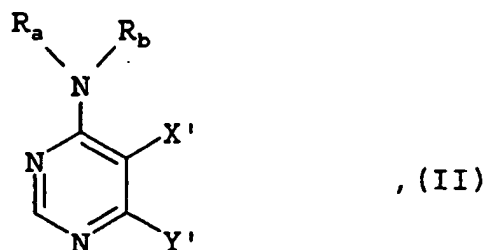
(17) 4-[(3-bromophenyl)amino]-6-({1-[(diethoxyphosphoryl)methyl]-piperidin-4-yl}amino)-pyrimido[5,4-d]pyrimidine,

(18) 4-[(3-bromophenyl)amino]-6-[(1-{[(ethoxy)(methyl)phosphoryl]methyl}-piperidin-4-yl)amino]-pyrimido[5,4-d]pyrimidine,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[trans-4-(2-oxo-morpholin-4-yl)-cyclohex-1-yl]amino}-pyrimido[5,4-d]pyrimidine

and the salts thereof.

7. Physiologically acceptable salts of the compounds according to claims 1 to 6 with inorganic or organic acids or bases.
8. Pharmaceutical compositions containing a compound according to claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.
9. Use of a compound according to at least one of claims 1 to 7 for preparing a pharmaceutical compositions which is suitable for treating benign or malignant tumours, for preventing and treating diseases of the airways and lungs, for treating polyps, diseases of the gastro-intestinal tract, the bile ducts and gall bladder and the kidneys and skin.
10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.
11. Process for preparing the compounds of general formula I according to claims 1 to 7, characterised in that
 - a) a compound of general formula



wherein

R_a and R_b are defined as in claims 1 to 6,
 X' and Y' together denote a

-N=CZ₁-CH=CH- ,
 -CH=N-CZ₁=CH- ,
 -CH=CZ₁-N=CH- ,
 -CH=CH-CZ₁=N- ,
 -N=CZ₁-N=CH- or
 -CH=N-CZ₁=N- bridge wherein

Z₁ denotes an exchangeable group, is reacted with a compound of general formula

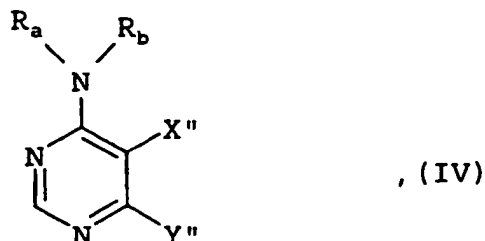


wherein

A and B are defined as in claims 1 to 6, or

b) in order to prepare a compound of general formula I wherein at least one of the groups R_6 to R_8 denote a hydrogen atom:

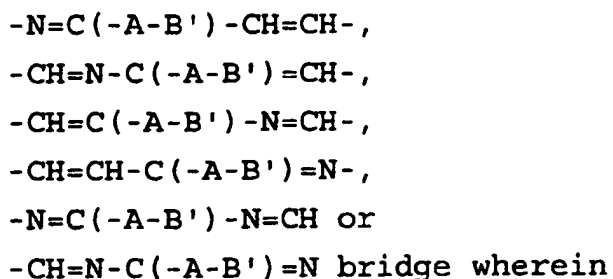
a compound of general formula



wherein

R_a and R_b are defined as in claims 1 to 6,

X'' and Y'' together denote a

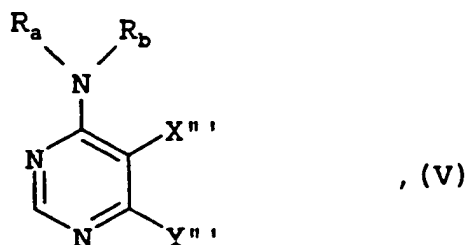


A is defined as in claims 1 to 6 and

B' has the meanings given for B in claims 1 to 6 with the proviso that B' contains an R_6O-CO , $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_8)$ group, wherein R_6 is defined as in claims 1 to 6 and at least one of the groups R_6 to R_8 does not represent a hydrogen atom, is converted by hydrolysis, treating with acids, thermolysis or hydrogenolysis into a compound of general formula I wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom, or

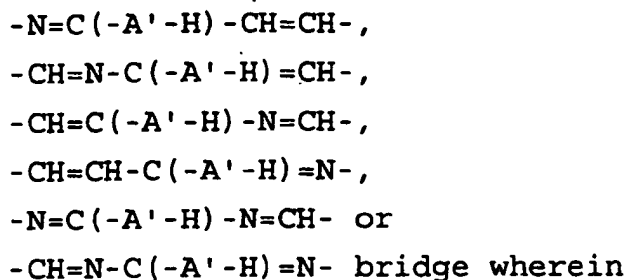
c) in order to prepare a compound of general formula I wherein A denotes an $-NR_4-C_{4-7}$ -cycloalkylene-NH-SO₂-CH₂CH₂ or $-NR_4-C_{4-7}$ -cycloalkylene-N(C₁₋₄-alkyl)-SO₂-CH₂CH₂ group and B denotes an $R_6O-CO-C_{1-6}$ -alkylene-NR₅ group, whilst R_4 to R_6 are defined as in claims 1 to 6:

a compound of general formula

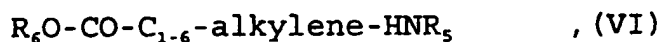


wherein

R_a and R_b are defined as in claims 1 to 6,
 X'' and Y'' together denote a



A' denotes an $-NR_4-C_{4-7}$ -cycloalkylene-NH-SO₂-CH=CH₂ or $-NR_4-C_{4-7}$ -cycloalkylene-N(C₁₋₄-alkyl)-SO₂-CH=CH₂ group, whilst R_4 is defined as in claims 1 to 6, is reacted with a compound of general formula

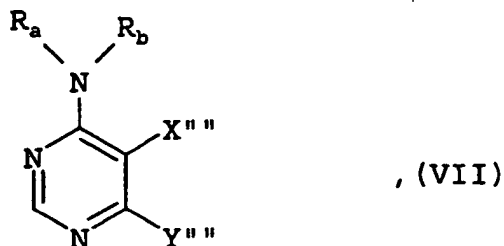


wherein

R_5 and R_6 are defined as in claims 1 to 6, or

d) in order to prepare a compound of general formula I wherein B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst in each case R_5 and R_6 are defined as in claims 1 to 6:

a compound of general formula



wherein

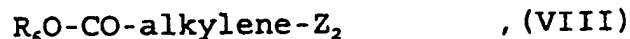
R_a and R_b are defined as in claims 1 to 6,

X'' and Y'' together denote a

-N=C(-A-B'')-CH=CH-,
 -CH=N-C(-A-B'')=CH-,
 -CH=C(-A-B'')-N=CH-,
 -CH=CH-C(-A-B'')=N-,
 -N=C(-A-B'')-N=CH- or
 -CH=N-C(-A-B'')=N- bridge, wherein

A is defined as in claims 1 to 6 and

B'' denotes an R_5 NH group wherein R_5 is defined as in claims 1 to 6, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, is reacted with a compound of general formula



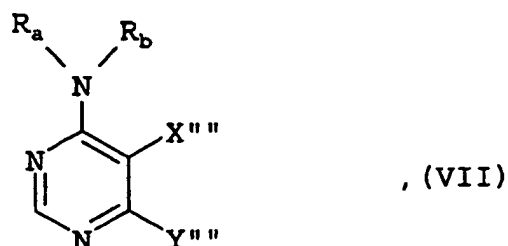
wherein

the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two $C_{1,2}$ -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group, whilst R_6 in each case is defined as in claims 1 to 6, and Z_2 denotes an exchangeable group, or

e) in order to prepare a compound of general formula I wherein B denotes an $(R_7O-PO-OR_8)-CH_2-NR_5$ or $(R_7O-PO-R_9)-CH_2-NR_5$ group,

a piperazino or homopiperazino group substituted in the 4 position by an $(R_7O-PO-OR_8)-CH_2$ or $(R_7O-PO-R_8)-CH_2$ group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by a $(R_7O-PO-OR_8)-CH_2$ or $(R_7O-PO-R_8)-CH_2$ group, whilst in each case R_5 and R_7 to R_9 are defined as in claims 1 to 6:

a compound of general formula



wherein

R_a and R_b are defined as in claims 1 to 6,

X''' and Y''' together denote a

$-N=C(-A-B'')-CH=CH-$,
 $-CH=N-C(-A-B'')=CH-$,
 $-CH=C(-A-B'')-N=CH-$,
 $-CH=CH-C(-A-B'')=N-$,
 $-N=C(-A-B'')-N=CH-$ or
 $-CH=N-C(-A-B'')=N-$ bridge wherein

A is defined as in claims 1 to 6 and

B'' denotes an R_5NH group wherein R_5 is defined as in claims 1 to 6, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, is reacted with formaldehyde or one of the derivatives thereof and a compound of general formula



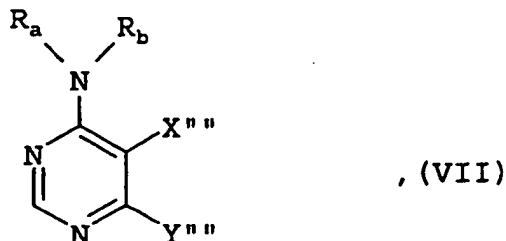
or C_{1-4} -alkoxy-P(R₇O)(R₈), (X)

wherein

R₇ to R₈ are defined as in claims 1 to 6, or

f) in order to prepare a compound of general formula I wherein B denotes an R₆O-CO-CH₂CH₂-NR₅ group wherein the -CH₂CH₂- moiety may be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an R₆O-CO-CH₂CH₂ group wherein the -CH₂CH₂- moiety may in each case additionally be substituted by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-CH₂CH₂ group wherein the -CH₂CH₂- moiety may in each case additionally be substituted by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group and R₅ and R₆ in each case are defined as in claims 1 to 6:

a compound of general formula



wherein

R_a and R_b are defined as in claims 1 to 6,

X'' and Y'' together denote a

-N=C(-A-B'')-CH=CH-,
 -CH=N-C(-A-B'')=CH-,
 -CH=C(-A-B'')-N=CH-,
 -CH=CH-C(-A-B'')=N-,
 -N=C(-A-B'')-N=CH- or

-CH=N-C(-A-B")=N- bridge wherein

A is defined as in claims 1 to 6 and

B" denotes an R₅NH group wherein R₅ is defined as in claims 1 to 6, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, is reacted with an acrylate of general formula



wherein

the vinyl moiety may be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group and R₆ in each case is defined as in claims 1 to 6, or

g.) a compound of general formula I wherein B denotes a piperidinyl group substituted in position 1 by a (R₇O-PO-OR₈)-CH₂CH₂ group:

a corresponding compound of general formula I containing a piperidinyl group unsubstituted in position 1 is reacted with a corresponding vinylphosphonic acid derivative, and

subsequently, if desired, a compound of general formula I thus obtained which contains a carboxy or hydroxyphosphoryl group is converted by esterification into a corresponding ester of general formula I and/or

a compound of general formula I thus obtained wherein B denotes an optionally substituted N-(2-hydroxyethyl)-glycine or N-(2-hydroxyethyl)-glycine ester group is converted by cyclisation into a corresponding 2-oxo-morpholino compound, and/or

if necessary any protecting group used during the reactions described above is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof.